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PECTIN AND GALACTURONIC ACID AND THE INTESTINAL PATHOGENS

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Previous work has strongly indicated that apple and pectin exert their favorable effect on diarrhea by way of their local action in the intestine.[1] The cellulose and lignin contained in apples must act as an absorbing colloid or mechanically, since they are not appreciably decomposed. The pectin, which is decomposed only in the colon,[2] could act similarly in the small intestine, but not in the colon, unless, as in the fasting dog, considerable pectin is not decomposed.[3] The local effect of pectin in the colon, therefore, is due to the action either of the intact molecule or of its decomposition products on pathogenic flora or their toxic or irritating products.

The chief products found to be formed in the decomposition of pectin were formic and acetic acids; either the quantity of galacturonic acid produced (pectin is a galacturonic acid complex) is small or it is decomposed as rapidly as it is formed.[4] In this paper studies are reported

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dealing with the effects of intact and decomposed pectin and galacturonic acid on the growth of a number of the major intestinal pathogens and on the toxin of Bacillus dysenteriae Shiga. The bacteriostatic and detoxifying properties of such volatile acids as formic and acetic have already been ascertained, and have been attributed to their p_H effect.[5] In addition, investigation of the aforementioned pathogens for their ability to break down pectin is reported.

GENERAL METHODS

Mediums.—The pectin and galacturonic acid used were the pure citrus variety employed in our previous work and were obtained from the research department of the California Fruit Growers' Exchange. The pectin is essentially free of such impurities as pentoses, pentosans, pigment and other materials frequently found in pectins. The galacturonic acid used is an enzymatic product of citrus pectin.[6]

Our liquid mediums containing pectin and galacturonic acid in combination with peptone we have respectively designated as "pectone" and "galactone." Both have been described.[4] Peptone alone was used as a control medium and was made up to contain 1 per cent peptone and 0.5 per cent sodium chloride. Broth instead of peptone was used in combination with pectin in the study of the decomposition of pectin by the intestinal pathogens. Broth alone was the control. For the work dealing with the growth of the intestinal pathogens, when a solid medium was necessary we utilized Endo's medium.

Autoclaving sufficient to bring about sterilization decomposes small quantities of pectin. Therefore, pectin-containing mediums to be used for the study of decomposition of pectin by bacteria were sterilized by Berkefeld filtration.[4] However, in the study of the effect of pectin, galacturonic acid and their decomposition products on the growth of the intestinal pathogens, autoclaving at 10 pounds (4.5 Kg.) for twenty minutes was the method of choice, since the small amount of breakdown could not interfere with the results of this study. The difficulties encountered in Berkefeld sterilization of highly viscous fluids are known. Autoclaving is the better method when it can be done safely.

Physical and Chemical Methods.—The decomposition of pectin by the intestinal pathogens was examined by the determination of relative viscosity, pectate formation, titratable acidity and p_H. The relative viscosity was determined by observing the time necessary for the fermenting fluids to pass through a 10 cc. pipet, to the lower end of which a capillary tube had been fused. Distilled water passed through in thirty seconds at room temperature of 30 C. Pectate formation was carried out by the calcium pectate method.[7] Titratable acidity was determined with tenth-normal sodium hydroxide solution and phenolphthalein as indicator, 10 cc. of the fermenting fluids being used. Determinations of p_H in this experiment, as in the others to be described, were made with a glass electrode. The value of these methods was dealt with in a previous publication.[4]

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RESULTS

The Effect of Intestinal Pathogens on the Decomposition of Pectin.—In these experiments the broth and pectin medium was used. After sterilization it was transferred aseptically in equal volumes to small Erlenmeyer flasks and then inoculated with fresh, pure cultures of the following organisms (broth alone, as a control, in similar flasks, was inoculated with the same organisms): (1) Bacillus typhosus; (2) Bacillus paratyphosus A; (3) Bacillus paratyphosus B; (4) Bacillus dysenteriae Flexner; (5) Bacillus dysenteriae Shiga; (6) Bacillus dysenteriae Sonne. Incubation was carried out for forty-eight hours at 37 C. This period was chosen because our previous work indicated

TABLE 1.—*The Effect of the Intestinal Pathogens on the Decomposition of Pectin*

Medium	Organism	(H)* Potentiometer	Titratable Acidity of Cc. of 0.1 N NaOH	Pectate in Gm.	Viscosity in Time
		Before Incubation			
* P and B	Uninoc.	7.0	2.80	0.88	59″
B	Uninoc.	7.3	1.00	0.00	31″
		Incubation for 48 Hours			
P and B	Uninoc.	6.9	2.80	0.87	58″
B	Uninoc.	7.2	1.00	0.00	32″
		Inoculated and Incubated for 48 Hours			
P and B	1	6.9	2.10	0.87	58″
B	1	7.4	0.70	0.00	31″
P and B	2	7.0	2.00	0.86	59″
B	2	7.45	0.75	0.00	33″
P and B	3	7.7	0.40	0.88	58″
B	3	8.0	0.00	0.00	31″
P and B	4	6.8	2.20	0.85	56″
B	4	7.4	0.80	0.00	30″
P and B	5	7.35	0.90	0.86	59″
B	5	7.35	0.85	0.00	32″
P and B	6	7.45	0.75	0.87	57″
B	6	7.40	0.80	0.00	33″

* P indicates pectin; B, broth.

that if any activity is present evidence of decomposition can be observed by then. At the end of this period the fermenting fluids were examined by the physical and chemical methods already referred to. The results are presented in table 1.

From the table one may observe that none of the bacteria used brought about the decomposition of pectin. The determination of hydrogen ion concentration and of titratable acidity revealed a reaction in the neighborhood of neutrality in all instances. Since the decomposition of pectin is accompanied by the production of acid,[8] this can be significant. Nevertheless, by themselves these values cannot be used to show that no acid was produced, for an initial production of acid could in two days be neutralized by the subsequent formation of alkali. However, in these experiments the absence of an acid reaction is confirmatory evidence that decomposition of pectin did not take place,

because no reduction of pectate formation or of relative viscosity was observed. Reduction in pectate formation and of relative viscosity is direct evidence of decomposition of pectin.

Intestinal Pathogens in Combination with Bacteria Capable of Decomposing Pectin.—In another experiment we compared the decomposition of pectin by the joint action of three isolated organisms known to liquefy pectin in combination with one of the aforementioned pathogens. It was thought that the addition of the pathogen might in some way influence the decomposition of pectin by the pectin-decomposing organisms.

The isolated organisms which liquefy pectin belong to the following groups: Aerobacillus, Micrococcus and Enterococcus.[4] In our previous work we have noted that they decompose pectin slowly. Even when they are in combination and after incubation for seven days complete liquefaction of pectin (no pectate formation) does not take place. However, the combination of the pectin-liquefying organisms with any one of the pathogens used in the studies reported in this paper resulted in complete liquefaction within five days. Thus, it is certain that the intestinal pathogens studied facilitate the liquefaction of pectin by pectin-liquefying organisms.

The Effect of Pectin, Galacturonic Acid and Their Decomposition Products on the Growth of Intestinal Pathogens.—What bacteriostatic or bactericidal activity pectin and galacturonic acid may possess could be due to a property of their intact molecules or to their influence on the p_H of the medium. Both are strongly acid in water solution, pectin having a p_H of 3 to 4 and galacturonic acid of 2 to 3. Such activity could be explained also by the formation of acids in their decomposition.[4] The experiments which follow were designed to ascertain any effect they may have on the growth of intestinal pathogens and to determine the mechanism of the action.

Non-neutralized "pectone" and "galactone," with peptone as a control, were first tried. The mediums were transferred aseptically to small Erlenmeyer flasks in 70 cc. amounts and inoculated with 0.1 cc. of a fresh broth culture of the pathogens previously mentioned. The p_H of the various mediums before inoculation was as follows: peptone, 6.0; "pectone," 3.75; "galactone," 2.85. After incubation for twenty-four hours, pour plates were made with 0.1 cc. of a 1:10 dilution in plain broth from each flask. After twenty-four hours' incubation the colonies on the plates were counted. The results are shown in table 2 *A*. Growth occurred in the peptone but did not take place in either the "pectone" or "galactone" medium.

Neutralized peptone, "pectone" and "galactone" were next tried. The results are presented in table 2 *B*. Abundant growth was observed in each medium.

To determine the effect of the decomposition products of pectin and galacturonic acid, the neutralized mediums were for twenty-four hours subjected to the action of the bacteria in a suspension of feces from a dog on a pectin diet.[7] At the end of the period the decomposed but non-neutralized mediums were sterilized and inoculated with the pathogens as previously described. The p_H of the various mediums before inoculation was as follows: peptone, 6.2; "pectone," 6.2; "galactone," 5.2. The results are given in table 2 *C*. In this experiment galacturonic acid exerted strong inhibition, while pectin had little if any influence on the growth of the organisms, except in the cases of B. typhosus and B. dysenteriae Shiga.

TABLE 2.—*The Effect of Intact and Decomposed Pectin and Galacturonic Acid on the Growth of Intestinal Pathogens*

Medium	Uninoculated Control	Organism 1	2	3	4	5	6
A. Non-Neutralized and Nondecomposed Mediums							
Peptone control....	Sterile	Innum.*	Innum.	Innum.	Innum.	Innum.	Innum.
Pectone	Sterile	0	0	0	0	0	0
Galactone	Sterile	0	0	0	0	0	0
B. Neutralized, Nondecomposed Mediums							
Peptone control....	Sterile	Innum.	Innum.	Innum.	Innum.	Innum.	Innum.
Pectone	Sterile	Innum.	Innum.	Innum.	Innum.	Innum.	Innum.
Galactone	Sterile	Innum.	Innum.	Innum.	Innum.	Innum.	Innum.
C. Mediums not Neutralized After Decomposition							
Peptone control....	Sterile	Innum.	Innum.	Innum.	Innum.	14	Innum.
Pectone	Sterile	300	Innum.	Innum.	Innum.	0	Innum.
Galactone	Sterile	2	0	0	0	0	13
D. Mediums Neutralized After Decomposition							
Peptone control.....	Sterile	Innum.	Innum.	Innum.	Innum.	Innum.	Innum.
Pectone	Sterile	Innum.	Innum.	Innum.	Innum.	3	Innum.
Galactone	Sterile	500	Innum.	Innum.	Innum.	0	Innum.

* Number of colonies on Petri dish at end of twenty-four hours.

It was apparent at this point that we were dealing with a p_H effect. Another experiment, therefore, like the one just described was performed, except that the mediums after decomposition and before incubation with the pathogens were adjusted to p_H 7.0. Table 2 *D* depicts the findings. All the organisms but B. dysenteriae Shiga grew well. That organism did not grow well in "pectone," "galactone" or peptone.

The Effect of Pectin and Galacturonic Acid on the Potency of Shiga Toxin.—The purpose was to study the possible detoxifying action of pectin and galacturonic acid on the toxin of B. dysenteriae Shiga.

The study was made with mixed materials incubated at 37 C. for twelve hours. These included the following combinations mixed in equal volumes: (*a*) pectin and saline solution; (*b*) galacturonic acid and saline solution; (*c*) broth and saline solution; (*d*) toxin and saline solution; (*e*) pectin and toxin; (*f*) galacturonic acid and toxin. Physiologic

TABLE 3.—*The Effect of Pectin and Galacturonic Acid on the Potency of Shiga Toxin in Rabbits*

No. of Rabbit	Weight in Kg.	Mixture Injected	Quantity Injected in Cc.	Comments
		Experiment A		
1	1.2	Toxin and saline solution	2.4	Diarrhea and paralysis at 7 hours; convulsions at 9; dead at 11
2	1.5		3.0	Dead at 19 hours
3	1.07		2.2	Dead at 2 hours
4	1.2		2.4	Dead at 4 hours
5	1.46		2.9	Dead at 18 hours
6	1.69	Pectin and saline solution	3.4	
7	1.42		2.8	
8	1.69		3.4	Alive after 2 weeks
9	1.6		3.2	
10	1.75		3.5	
11	1.19	Galacturonic acid and saline solution	2.4	
12	1.38		2.8	
13	1.49		3.0	Alive after 2 weeks
14	1.98		4.0	
15	1.38		2.8	
16	1.7	Broth and saline solution	3.4	
17	1.47		2.9	
18	1.78		3.6	Alive after 2 weeks
19	1.0		2.0	
20	1.74		3.5	
21	1.6	Pectin and toxin	3.2	Dead at 7 hours
22	1.44		2.9	Dead at 7 hours
23	1.59		3.2	Diarrhea and paralysis at 20 hours; dead at 32 hours
24	1.67		3.3	Diarrhea and paralysis at 20 hours; dead at 30 hours
25	1.57		3.2	Dead at 18 hours
26	1.47		2.9	Dead at 3 hours
27	1.65		3.3	Dead at 4 hours
28	1.44		2.9	Dead at 19 hours
29	1.29		2.6	Dead at 3 hours
30	1.29		2.6	Dead at 19 hours
31	1.55	Galacturonic acid and toxin	3.1	Alive after 2 weeks
32	1.69		3.4	Alive after 2 weeks
33	1.76		3.5	Alive after 2 weeks
34	1.27		2.5	Dead at 72 hours
35	1.4		2.8	Dead at 72 hours
36	1.37		2.7	Dead at 60 hours
37	1.9		3.8	Alive after 2 weeks
38	2.43		4.9	Alive after 2 weeks
39	1.75		3.5	Dead at 54 hours
40	1.72		3.4	Dead at 64 hours
		Experiment B		
41	1.69	Toxin and saline solution	3.4	Dead at 6½ hours
42	1.7		3.4	Dead at 6 hours
43	1.49		3.0	Dead at 1½ hours
44	1.38		2.8	Dead at 1 hour
45	1.75		3.5	Dead at 2 hours
46	1.46	Galacturonic acid and toxin	2.9	Alive 2 weeks later
47	1.69		3.4	Dead at 27½ hours
48	1.64		3.3	Alive 2 weeks later
49	1.6		3.2	Dead at 26 hours
50	1.55		3.1	Dead at 28 hours
51	1.42	Neutralized galacturonic acid and toxin	2.8	Dead at 2½ hours
52	2.32		4.6	Dead at 12 hours
53	1.98		4.0	Dead at 6½ hours
54	1.78		3.6	Dead at 2½ hours
55	1.74		3.5	Dead at 2½ hours

solution of sodium chloride, 2 per cent pectin and 2 per cent galacturonic acid were used. The pectin, galacturonic acid and broth were autoclaved, while the toxin was obtained by Berkefeld filtration of a four day broth culture of the organism. Intravenous injections into normal rabbits were carried out with these mixtures in a dose of 2 cc. per kilogram of body weight.

Table 3 presents the results. The data on experiment A indicate that pectin, galacturonic acid and broth, given to rabbits 6 to 20 inclusive, are not toxic, but that the Shiga toxin, given to rabbits 1 to 5 inclusive, is lethal in the dose used within twenty-four hours. No detoxifying action by pectin is observed. The rabbits which received the pectin and toxin mixture all died during the first twenty-four hours after injection. The results obtained with galacturonic acid and toxin, on the other hand, indicate some detoxifying activity. Five of the rabbits died from fifty-four to seventy-two hours after the injection, while 5 were still alive two weeks later. Since these results may be due to the low p_H of the mixture (3.0) rather than to any property of the galacturonic acid molecule, it was decided to repeat this portion of the experiment with the addition of a mixture of neutralized galacturonic acid and toxin. The results obtained in this experiment (experiment B) are likewise given in table 3. The lethal action of the toxin is again observed from the data on the rabbits 41 to 45 inclusive. Detoxifying activity by the galacturonic acid is again indicated, but when the acid is neutralized the action is lost. Rabbits 51 to 55 inclusive, which received a mixture of neutralized galacturonic acid and toxin, died within six and a half hours, as did those which received the toxin alone.

COMMENT

It is apparent from the results that the intestinal pathogens studied are not able to decompose the large pectin molecule. The chemical and physical methods used to determine decomposition indicated no change in structure. The more rapid decomposition of pectin by the combination of organisms known to liquefy pectin with any one of the intestinal pathogens studied is also evident. A ready explanation of the phenomenon, however, is not available. It is possible that the base produced by the pathogen acting on the protein in the medium offsets the acid produced in the decomposition of pectin sufficiently to maintain a reaction more favorable for the growth of the pectin liquefiers. In other words, the relatively slow liquefaction of pectin by even a combination of these organisms is probably due to limitation of their growth by the acid produced in the decomposition of pectin.

The experiments dealing with the possible influence of pectin, galacturonic acid and their decomposition products on the growth of

intestinal pathogens indicate that they exert at least an inhibiting effect. This is due to their influence on the p_H of the medium. The degree of bacteriostasis would depend on how much the p_H had been lowered. In fact, the p_H of the medium could be lowered to the point where it might be considered bactericidal, as in experiment A shown in table 3. However, in the instance of B. dysenteriae Shiga a factor, or factors, in addition to p_H appears to be operating to limit the growth of this organism. The most likely explanation is either a depletion of some necessary food elements or the production of an antagonistic substance.

The influence of pectin on p_H may be used to explain its local action in the colon and its favorable effect on diarrheas caused by the intestinal pathogens. Since a water solution of pectin has an acid p_H ranging from 3 to 4, and since the decomposition of pectin is associated with the production chiefly of volatile acids, a bacteriostatic effect is possible. A p_H of 3 is probably rarely reached in the colon even with pectin present in fairly large amounts, because the base or alkali readily formed in the colon from protein would tend to neutralize the acid reaction of pectin and its decomposition products. However, we have reported finding the p_H of the colons of dogs fed pectin as low as 5.0.[4] Such a p_H is not favorable to the growth of the intestinal pathogenic bacteria.

The toxin of B. dysenteriae Shiga was not detoxified by pectin. Non-neutralized galacturonic acid appeared to manifest definite detoxifying activity. The p_H of the mixture of galacturonic acid and toxin incubated for twelve hours at 37 C. was 3.0. Neutralized galacturonic acid, however, did not modify the potency of the toxin. The detoxifying action of non-neutralized galacturonic acid, then, may be ascribed to its acidity.

CONCLUSIONS

The following intestinal pathogens are not able to liquefy pectin: B. typhosus; B. paratyphosus A; B. paratyphosus B; B. dysenteriae Flexner; B. dysenteriae Shiga; B. dysenteriae Sonne. However, the addition of any one of these pathogens to a combination of organisms known to liquefy pectin is associated with a more rapid decomposition of pectin than that observed with the combination alone.

Pectin, galacturonic acid and their decomposition products manifest bacteriocidal as well as a bacteriostatic activity on intestinal pathogens. This is due to the acidity of pectin and its decomposition products. The influence of pectin on the p_H of the intestinal contents is the most probable explanation of the favorable effect of pectin on diarrheas caused by the intestinal pathogens.

Pectin does not detoxify the toxin of B. dysenteriae Shiga. The observed detoxifying action of non-neutralized galacturonic acid is ascribed to its acidity.

MONOZYGOSITY IN MONGOLOID TWINS

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Monozygotic (or identical) twins among mongoloid imbeciles are rarely encountered. Of 16 reported cases of mongolism in both twins of the same sex (table 1), 3 of the pairs have been described as dizygotic

TABLE 1.—*Sixteen Cases of Mongolism in Both Twins of the Same Sex*

Number	Date	Authority	Sex of Twins	Type of Twins
1	1902	de Bruin	♂ ♂	Monozygotic
2	1909 1926	Hjorth Krabbe	♀ ♀	Monozygotic
3	1923	Strauch	♂ ♂	Monozygotic
4	1926	Brückner	♀ ♀	Monozygotic
5	1926 1935	Reuben & Klein Leader & Grozin	♂ ♂	Monozygotic
6	1927	Dickey	♂ ♂	Monozygotic
7	1930	Bauer	♀ ♀	Monozygotic
8	1930	Strausky	♀ ♀	Monozygotic
9	1932	Blechmann, Guillaumin, & Karmann	♂ ♂	Monozygotic
10	1933	Russell	♀ ♀	Dizygotic
11	1933	Lund	♀ ♀	*Monozygotic
12	1934	Rosanoff & Handy	♀ ♀	Monozygotic
13	1934	Penrose	♂ ♂	Monozygotic
14	1935	Frumkin	♀ ♀	Monozygotic
15	1936	MacKaye	♂ ♂	Dizygotic
16	1938	Gordon & Fraser	♂ ♂	*Dizygotic

* Adequate analysis of type of twinning.

and the remaining 13 as monozygotic. In the accounts of these cases, however, an adequate analysis of the type of twinning was given only by Lund and by Gordon and Fraser; so the true proportion of types is still a matter of doubt. The case to be reported here has been previously discussed by one of us (Miss Frumkin) from the psychologic angle, but no biologic analysis of the twins was made. Dr. Elizabeth Nesbitt brought us together.

The biologic study of twins usually gives an accurate determination of the type of twinning (whether identical or fraternal), and in the case

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of twins with mongolism this analysis is most desirable before final conclusions are reached regarding the causation of mongolism. The determinations of the type of twinning are based on comparisons of a number of physical characters (particularly skin patterns), all of which have been demonstrated to possess high reliability.

A new significance has been given to the study of twins with mongolism by the recent discovery of Dr. Harold Cummins, who showed

Fig. 1.—Monozygotic twins with mongolism, A and K, aged 13 years.

that in the palm and finger patterns of mongoloid imbeciles there are distinct trends which characterize the group. Certain palmar patterns (known as loop ulnars, L^{u}) occur in over one third of mongoloid imbeciles, as against about one fiftieth of normal persons; other patterns (arch carpals, A^{c}) are found in about one eighth of mongoloid imbeciles, as against one in every hundred normal persons. Trends are found also in the finger patterns. These disturbances in growth of skin patterns *time* the disturbance in the development of the fetus and indicate

that it must have been occurring before the third or fourth fetal month, for during that period the development of the dermal ridges is completed. The work of Cummins was confirmed and extended by Workman. Whether the disturbance is entirely environmental or in part genetic remains to be established.

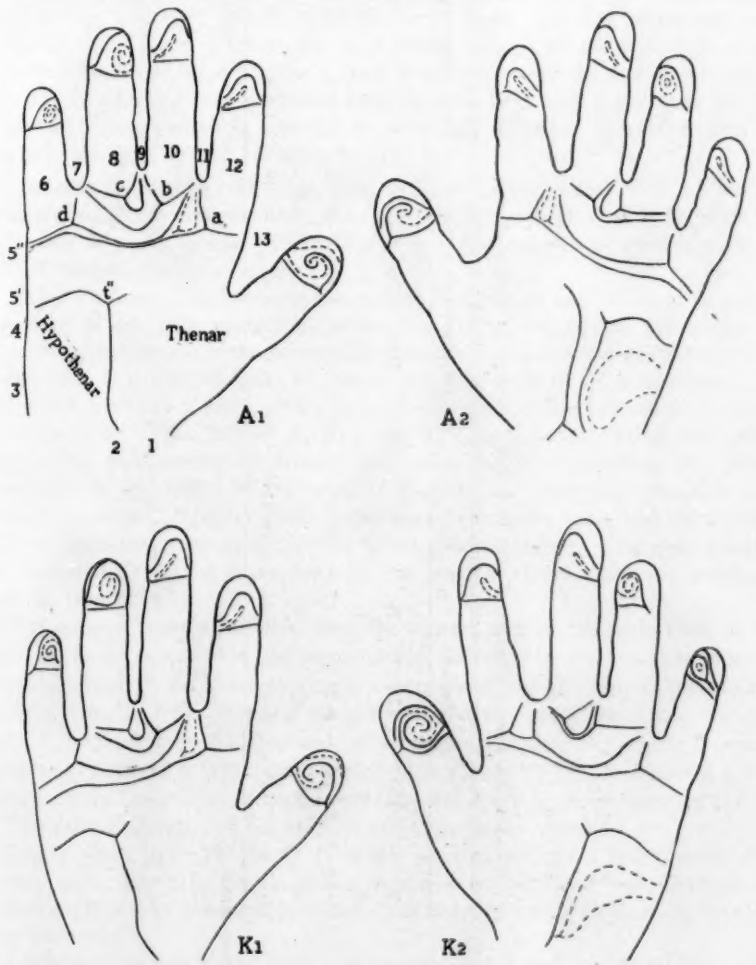

Fig. 2.—Outline drawings of palmar prints of twins A and K. *A 1* and *A 2*, left and right palms of twin A; *K 1* and *K 2*, left and right palms of twin K.

TABLE 2.—*Palmar Formulas of Twins A and K*

A.	Left	11(12).	9 . 7 .	5" (6)—t"—A^c .	O. D. L. M.
	Right	11 .	9 . 7 .	5" —tt"—L^a .	O. D. L. M.
K.	Left	11 .	9 . 7 .	5" —t"—A^c .	O. D. L. M.
	Right	13(12).	11(10). 9(8).	11/7(6)—tt"—L^a(V).	O. D. L. M.

TABLE 3.—*Finger Pattern Types and Ridge Counts of Twins A and K*

Twin		Left Fingers V	IV	III	II	I	Quantitative Value Lt.	Total	Rt.	Right Fingers I	II	III	IV	V
A	Pattern	W	W	U	U	W				W	U	U	W	U
	Ridge Count	13-18	23-21	0-20	0-17	20-24	102	178	76	23-12	6-0	18-0	14-20	9-0
K	Pattern	W	W	U	U	W				W	U	U	W	W
	Ridge Count	15- 5	17-20	0-17	0-17	18-21	90	177	87	23-16	19-0	19-0	15-17	9-7

Symbols: W, whorl; U, loop ulnar.

Since mongoloid imbeciles in general show these distinct and restricted trends in their dermatoglyphic patterns, it is interesting to examine and compare the dermal patterns of a pair of twins with mongolism.

REPORT ON TWINS

Family History.—The twins, A and K (fig. 1), are girls with mongolism, 13 years of age, who have been cared for by their present "guardian" since they were 3 months old. Little is known of their family history, although there is reason to believe that they were born at a sixth pregnancy, when the mother was 49 or 50 years of age, and that there had been an interval of nine years since her last pregnancy. The mother is reported to have died following their birth, and the sibs are said to be normal (Frumkin).

Dermatoglyphic Patterns.—The palm and sole prints of the twins, as well as some anthropologic measurements, were made in July and October 1939, when the girls were 13 years of age. This material was supplemented by records made by Miss Frumkin five years earlier.

Palm Patterns: In studying the palmar patterns of any hand, of a normal person or of one with mongolism, certain main lines and triradii are traced out in the dermal ridges according to standard methods (Cummins and associates, 1929). A triradius is a meeting point of dermal ridges passing in three directions, and typically a triradius is found at the base of each finger. The triradii at the bases of digits II to V are lettered A, B, C and D (fig. 2, *A 1*). Along the central axis of the palm additional triradii may occur in three positions, viz. at the wrist (t), in the center of the palm (t″) or in an intermediate position (t′). From each digital triradius a main line is traced across the palm, and the terminations of these lines are recorded briefly in the palmar formula. The areas marking the terminations of the main lines on the margin of the palm are numbered 1 to 13 (fig. 2, *A 1*).

The palmar formula includes, first, the terminations of the main lines, in the order D, C, B, A, and then the axial triradii, followed by symbols descriptive of patterned areas, in the order hypothenar, thenar and first interdigital, interdigitals II to IV (fig. 2, *A 1*). Some of the symbols used for pattern areas are: O, open field; A, arch; L, loop; D, loop with an accessory triradius; W, whorl; U, ulnar; C, carpal. Suffixes indicate the direction of a pattern; e. g. L^u describes a loop opening to the ulnar side. Alternate readings are given in parentheses, as 11(12).

The palmar formulas of the twins A and K are given in table 2.

Finger Patterns: The study of finger patterns and their ridge counts is a subject more generally known and understood, having been well described by Bonnevie (1924), by Newman, by Wentworth and Wilder, by Hoover and by many other authors.

In the twins A and K, the finger patterns are homolaterally comparable throughout the ten digits, with one exception (Rt. V). Only two types of patterns occur, viz., whorls (W) and ulnar loops (U) (fig. 2; table 3). The total ridge counts of these patterns for the twins are 178 and 177, showing thus the slight difference of one ridge (table 3).

Sole and Toe Patterns: The plantar patterns of the foot are recorded similarly to those of the palm, the formula including the main line terminations, D, C, B and A, as well as a main line from the hallucal triradius, followed by the pattern areas, hypothenar, calcar, thenar, hallucal and interdigitals II to IV (fig. 3, *A 1*) (method devised by MacArthur and Ford).

The plantar formulas for the twins A and K are given in table 4.

Toe patterns and their ridge counts are recorded in the same manner as finger patterns, and the readings for the twins A and K are given in table 5.

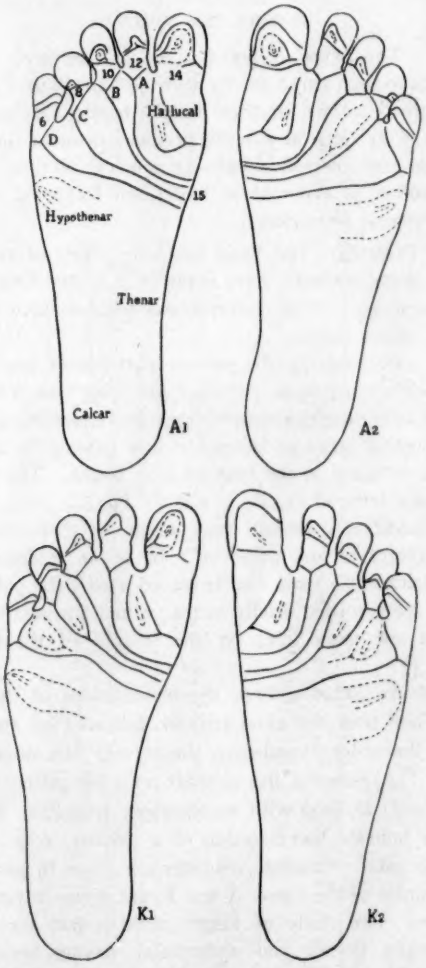

Fig. 3.—Outline drawings of plantar prints of twins A and K. *A 1* and *A 2*, left and right soles of twin A; *K 1* and *K 2*, left and right soles of twin K.

TABLE 4.—*Plantar Formulas of Twins A and K*

Below the hallucal symbol is given the ridge count of its pattern, and below other symbols are recorded accessory deltas (d). Symbols: L^t, loop tibial; L^d, loop digital; O, open field.

A.	Left	15.	15 .	15.	15.	13.	L^t.	O.	O.	L^d . 0-20	O.	O .	O .
	Right	15.	15 .	15.	15.	13.	L^t.	O.	O.	L^d . 19-0	O.	L^d. d	O .
K.	Left	15.	15/9.	15.	15.	13.	L^t.	O.	O.	L^d . 0-14	O.	L^d. d	L^d. d
	Right	15.	15/9.	15.	15.	13.	L^t.	O.	O.	L^d . 21-0	O.	L^d. d	L^d. d

TABLE 5.—*Toe Patterns and Ridge Counts of Twins A and K*

Twin		Left Toes					Quantitative Value			Right Toes				
		V	IV	III	II	I	Lt.	Total	Rt.	I	II	III	IV	V
A	Pattern	A	F	W	T.A	W				W	F	F	F	A
	Ridge Count	0	0-1	9-8	0	12-24	34	68	34	24-15	4-0	4-0	2-0	0
K	Pattern	A	A	F	F	W				F	F	F	A	A
	Ridge Count	0	0	0-6	0-6	11-20	32	69	37	25-0	6-0	6-0	0	0

Symbols: A, arch; T.A., tented arch; W, whorl; F, fibular loop.

EVIDENCE OF MONOZYGOSITY

In the analysis of the data on these twins with mongolism (A and K) a number of comparisons can be made to demonstrate the monozygosity of their origin. These are as follows:

1. In the study of dermal patterns a generally accepted criterion of monozygotic twinning is that the difference between the right and the left hand of either twin should be greater than the difference between two corresponding hands of the pair of twins. This diagnostic rule holds true for the twins A and K, for whom the bilateral difference in a series of palmar measurements is 24.8 per cent for A and 28.6 per cent for K, while the homolateral difference between the twins is only 18.4 per cent (table 6).

2. The amount of homolateral difference (18.4 per cent) in the palmar patterns of the twins A and K is within the range found to

TABLE 6.—*Percentile Differences Between Hands of Twins A and K as Compared with Averages for Identical and Fraternal Twins*

Homolateral differences for (1) ridge counts of the fingers, (2) finger pattern types, (3) main lines and axial triradii, (4) palmar patterns. Percentages for identical and fraternal twins from MacArthur and Ford.

	(1)	(2)	(3)	(4)	Average
Twins A and K	17.4	10.0	45.0	1.2	18.4
Identical twins	8.0	19.0	28.0	21.0	19.0
Fraternal twins	30.0	44.0	41.5	36.5	37.9
Bilateral Differences					
Twin A	39.3	20.0	20.0	20.0	24.8
Twin K	4.5	0.0	90.0	20.0	28.6

obtain for identical twins generally (19.0 per cent) and is inconsistent with the much greater difference found in fraternal twins (37.9 per cent) (table 6).

3. According to Bonnevie (1931) and Steffens, ridge numbers and the distribution of ridge counts in finger and toe patterns are inherited characters. The genotypes may be approximately determined as follows:

Fingers	Toes
Maximum number of ridges on any digit	
VV (0 -15)	VV (0 -15)
Vv (16-21)	Vv (16-24 or 25)
vv (22- x)	vv (25 or 26- x)
Ridge count on any one of digits I, II and III below maximum	
rr (0- 4)	tt (0- 4)
Rr (5-10)	Tt (5-10)
RR (11- x)	TT (11- x)
Ridge count on digit IV or V below maximum	
uu (0- 4)	ff (0- 4)
Uu (5-10)	Ff (5-10)
UU (11- x)	FF (11- x)

By these methods the genotypes for the fingers are vvRRUU for twin A and vvRrUU for twin K, and for the toes of each twin, VvTTFF. Except for the discrepancy in the radial group of digits, the genotypes offer another point of agreement consistent with a monozygotic origin.

4. Blood typing established the fact that both the twins belong to group O (type IV, Moss; type I, Jansky).

5. With respect to the following physical characters the twins A and K were given the same rating: by Schultz's chart, skin color (3), hair color (5), eye color (7); and by Hesch's chart, pigment pattern (7). Both twins had dark eyelashes of medium length, well developed eyebrows and straight hair. Tracings on ground glass were made of their ears, which were broadly oval, with a wide roll forming the superior helix, and had adherent lobes.[1]

TABLE 7.—*Comparison of Heights and Weights of Twins A and K Over a Period of Five Years*

Age	Twin K		Twin A	
	Height, Inches	Weight, Lb.	Height, Inches	Weight, Lb.
7 yr., 9 mo.	43¼	43	43⅜	41
8 yr., 7 mo.	45	49¼	45	44½
9 yr., 6 mo.	47¾	50	48¼	58
10 yr., 2 mo.	49	54½	49½	50½
10 yr., 8 mo.	51	57	50¾	52½
11 yr., 4 mo.	52½	63¾	52½	60¼
12 yr., 11 mo.	55	74½	55	73¼

6. In height and weight the twins have varied but slightly from each other over a growing period of five years (table 7).

It may therefore be concluded, both from the agreement with respect to a number of physical characters and from the evidence of the dermatoglyphic findings, that A and K are monozygotic twins.

Trends in the Dermatoglyphic Patterns Indicative of Mongolism.—The palmar patterns of the twins A and K are typically those of mongoloid imbeciles, conforming to the distinct trends which Cummins (1936; 1939) elucidated and Workman confirmed. These trends, as they appear in the twins, are summarized in table 8. They are seen:

1. In the hypothenar patterns, where a loop opening to the ulnar side is found in the right hands of A and K (fig. 2). This pattern occurs in over one third of persons with mongolism, as compared with only one fiftieth of normal persons. A second type of hypothenar pattern, viz. the arch opening to the wrist (A^c, seen in the left hands of

1. The fact that one twin (A) is left handed and the other right handed has no special significance regarding monozygosity, since left-handedness is equally common in identical and fraternal twins (Wilson and Jones; Rife).

A and K) is present in about one eighth of persons with mongolism, as against one of every hundred normal persons.

2. In the interdigital patterns, there being a higher frequency occurrence in the second and third interdigital areas and a lower frequency in the fourth area of persons with mongolism as compared with normal persons (13.8 per cent versus 4.2 per cent; 78.1 per cent versus 40.8 per cent; 28.8 per cent versus 49.0 per cent). The distribution of the interdigital patterns in the twins A and K is in keeping with these trends, all four hands possessing loops in the second and third areas (D and L) and none in the fourth area (M, classed as a patternless area).

3. In the unusual termination of line D at 13 in K's right hand (fig. 2). Rarely is this termination found in normal hands (Keith;

TABLE 8.—*Comparison of Percentile Frequencies in Hands of Mongoloid Imbeciles and of Normal Persons of Palmar Patterns Present in Twins A and K*

Patterns Present in the Twins A and K	Mongoloid Imbeciles: Average of Cummins and Workman (1939), Percentage	Normal Persons: Cummins (1935), Percentage
Hypothenar		
L^u (rt. hands of A and K)	33.2	1.6
A^c (lt. hands of A and K)	12.8	1.0
Interdigital		
II Interdigital, in all four hands	13.8	4.2
III Interdigital, in all four hands	78.1	40.8
IV Interdigital, none *	28.8	49.0
Line D, terminating at 13, right hand of K	2.5 (Ford)	0.24 (Average of Cummins and Midlo, Csik and Malan and Ford)

* M (an area of multiplication) is classed as a patternless area.

Cummins and Midlo). Csik and Malan cited a frequency occurrence of 0.36 per cent. In a survey of some 500 hands taken at random made by one of us (Dr. Ford) this termination occurred only once (0.2 per cent), while among 200 hands of persons with mongolism 5 examples have been noted (2.5 per cent), indicating, therefore, another trend in the patterns which characterize mongolism.

Regarding the plantar patterns no data are at present available for comparisons. (A study of the soles of persons with mongolism is in progress.)

SUMMARY

A résumé of 16 cases of mongolism in both twins of the same sex is given.

The twins A and K are shown to be monozygotic. (The conclusiveness of the data removes any doubt which may have been raised con-

cerning this point in the discussion of the paper presented by Frumkin in 1935.)

The effect of a prenatal disturbance in growth, before the third or fourth fetal month, is recorded in this pair of monozygotic twins. The record of the disturbance is found in certain of the palmar patterns, viz. the hypothenar and interdigital patterns and the termination of the line D.

The close intra-pair resemblance of the twins A and K leads to the inference that there is a genetic element in the causation of mongolism. If the condition were due entirely to an environmental disturbance, considerably more variation between even monozygotic twins would be expected. (Intra-pair differences in monozygotic twins due to a prenatal environmental factor have been recorded [Ford, Brown and McCreary].)

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ERYTHROBLASTIC ANEMIA FOLLOWING SPLENECTOMY IN CASES OF CHRONIC FAMILIAL HEMOLYTIC ANEMIA

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Splenectomy is claimed to be the best treatment of chronic hemolytic anemia. W. J. Mayo [1] said in 1916, "No other operation I know gives me more brilliant and striking results," and, again, in 1923, "The patient's improvement is little short of marvelous." In several cases of chronic hemolytic anemia that we have studied in which splenectomy was performed, the patient made a full recovery. In the last years, however, splenectomy has not given uniformly good results. W. P. Thompson [2] classified hemolytic jaundice into a typical and an atypical variety. Typical hemolytic jaundice is characterized by spherocytosis with increased fragility of the red cells. This variety responds well to splenectomy. Atypical hemolytic jaundice is characterized by absence both of spherocytosis and of increased fragility of the red cells. This variety does not respond well to splenectomy. In 1927 Roth [3] published a case in which in spite of splenectomy hemolytic or acute hemoclastic crises developed. A. P. Thompson [4] in 1932 observed persistent acholuric jaundice with increased fragility of the red cells following splenectomy. Dyke and Young [5] in 1936 observed 6 cases of macrocytic hemolytic anemia with increased fragility of the red cells in which there was only slight and temporary improvement after splenectomy. Freund [6] in 1932 published 2 cases in which hemo-

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lytic jaundice was not influenced by splenectomy. There seem to be some doubts as to the diagnosis in her second case. The first case was that of a boy 10 years of age suffering from congenital familial hemolytic jaundice with increased fragility of the red cells, urobilinogenuria, reticulocytosis and severe anemia. After splenectomy there were further lowering of the red cell count and of the hemoglobin values and an increase in the urobilinogenuria and in the icterus index, and the patient ultimately died of severe anemia. Pende [7] cited the case of Ceconi, in which the patient was not favorably influenced by splenectomy. The postmortem examination in that case revealed "numerose ghiandole emolinfatiche in uno stato d'iperattivitá e simili a la milsa eritrofagica dell ittero (many hemolymph glands in a state of hyperactivity and similar to the spleen in hemolytic jaundice)." Ceconi expressed the opinion that splenectomy can be without influence in a case of compensatory erythrolytic hyperfunction of the hemolymph glands.

There are characteristic changes in the blood that occur after splenectomy. Meulengracht [8] and Eppinger [9] observed the almost constant presence of Howell-Jolly bodies even for a long time after splenectomy and attributed their presence to the loss of the regulating function of the spleen on the maturation of the red cells in the bone marrow. Singer, Miller and Dameshek [10] recently wrote: "The presence of Howell-Jolly bodies (improper denucleation) after splenectomy suggests a possible relationship of the spleen to the extrusion of the normoblast nucleus." Schonboe [11] observed a girl of 16 years who had congenital syphilis and later presented symptoms of thrombosis of the splenic vein. She had severe anemia, with only 28 per cent hemoglobin (Sahli). In spite of the anemia there were no nucleated red cells in the peripheral blood. The bone marrow was normal. Splenectomy was performed, and she was doing well for almost sixteen months after operation, when she had a recurrence of the hemorrhage and died suddenly. Before death the reticulocyte count had gone up to 20 per cent and 34 per cent of the counted cells were nucleated red cells. The bone marrow was hyperplastic. Although before splenectomy, as already mentioned, there were no nucleated red cells in spite of the anemia, after splenectomy the peripheral blood was flooded with normoblasts. According to the author there is probably formed in the spleen a substance which, reaching the

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circulation without passing through the liver, inhibits the emission of the red blood cells from the bone marrow.

Erythroblastic response to splenectomy is well known in Mediterranean (Cooley's) anemia, also sometimes known as thalassemia. Wollstein and Kreidel,[12] Whipple and Bradford [13] and even Cooley [14] reported observations on this erythroblastic response. In the case of Wollstein and Kreidel [12] the erythroblastosis was observed until death, which took place five years after splenectomy. The proportion of erythroblasts was as high as 1,455 to 100 white cells, while in the case of Cooley the highest ratio was 2,200: 100. Even the white cell count (disregarding nucleated red cells) is high in these cases. Whipple and Bradford [13] reported as the highest counts 105,600 white and 222,000 nucleated red cells per cubic millimeter of blood. In Cooley's [14] case the highest counts were 21,500 white and 163,900 nucleated red cells. It is possible that the spleen has an effect on the white cell count, in view of the observations of Wiseman and Doan [15] on patients with chronic granulocytopenia who recovered after splenectomy. Baty, Blackfan and Diamond [16] summarized the results of splenectomy in cases of Mediterranean anemia. The erythrocyte count and the hemoglobin percentage remain essentially unaltered after splenectomy. Exceptionally there may be a slow and persistent increase. The total number of leukocytes and the percentage of immature forms increase rapidly from ten days to two weeks after operation and then decrease slowly to slightly above the preoperative level. The number of nucleated red cells rises sharply after splenectomy, remaining above the previous level and constituting from 50 to 90 per cent of the total nucleated cell count. There are a concomitant rise in the number of immature erythrocytes and an increase in the anisocytosis and poikilocytosis, so that it is often impossible to find a normal-appearing adult erythrocyte in the stained film of blood.

The study of the changes in the blood following splenectomy is of great interest. Through a careful examination of these changes one may get important data as to the probable nature of the hemolytic anemia. One should, however, be on the alert not to consider secondary changes resulting from the increased or decreased destruction of red cells as primary changes due directly to the removal of the spleen. For instance,

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Eppinger [9] stressed the importance of the decreased output of urobilinogen in the feces, the decreased excretion of uric acid in the urine and the increased cholesterol level in the blood serum. These changes are, however, due only to the decrease in destruction of the corpuscular elements of the blood. According to Meulengracht,[8] the main consequences of splenectomy are that (1) the anemia subsides, (2) the microcytosis subsides but not completely, (3) the fragility test tends to show near normal values, though not always, (4) the reticulocytes diminish or disappear from the blood, (5) there is constantly a large number of Howell-Jolly bodies after splenectomy, (6) the platelet count is increased transitorily, (7) the jaundice diminishes or soon disappears and (8) the hyperactivity of the bone marrow subsides. All of these changes are due to the cessation of the exaggerated destruction of the corpuscular elements of the blood by the spleen. Should these changes be constant, then the etiologic importance of the spleen for the disease would be well established.

There are, however, cases reported in the literature in which these changes are not observed after splenectomy. In this report we are giving our observation on 2 cases in which chronic familial hemolytic anemia did not respond well to splenectomy and the blood did not show the changes described by Meulengracht. While the spleen undoubtedly plays an important role in the pathogenesis of this disease, there may be, from our observations, certain other factors prevailing which prevent the improvement that is expected after splenectomy. There must be in the spleen a substance that is responsible for the maturation and denucleation of the red cells in the bone marrow. We have already mentioned the observation of Schonboe [11] of erythroblastosis following splenectomy and of Singer, Miller and Dameshek [10] of the presence of Howell-Jolly bodies, emphasized even by Meulengracht. Such changes are generally noted after splenectomy in cases of Mediterranean anemia. If there is such a function in the spleen, erythroblastosis might be observed in association with other types or varieties of hemolytic anemia. A question would, however, arise as to how long such erythroblastosis would remain. On this question our interest is again focused.

We shall now describe a case in which we observed erythroblastosis of very short duration appearing after splenectomy:

A. de L., a 23 year old man, single, a farmer, was admitted to the medical service of the Philippine General Hospital first in March 1940, because of frequent, sometimes almost daily, attacks of chills, fever and sweating, which he had had for five years. Each attack would last for a few hours, and there were sometimes accompanying headache, pains in the chest and back and slight rigidity with vague pains in the left hypochondrium. On admission to the hospital he was informed of the presence of a mass on the left side of the abdomen and of a slight yellowish discoloration of his scleras, of which he had had no cognizance. After a month's stay in the hospital he was discharged improved, and he had since then remained symptomless except for the presence of the mass in the left half of the abdomen,

which, according to him had slightly increased in size. A month before his second admission, on Aug. 27, 1941, he had a recurrence of the attacks of chills, which were accompanied with slight fever and headache and took place daily, lasting for a few hours. At this admission the most important findings on physical examination were the presence of slight jaundice and an enlarged spleen extending to about 3 fingerbreadths below the umbilical level and about 2 fingerbreadths lateral to the median line toward the right.

Examinations of the peripheral blood by a student gave the following results:

Date	Red Cells	Hemoglobin, per Cent (Tallqvist)	White Cells: Total Count	Neutrophils, per Cent	Eosinophils, per Cent	Lymphocytes, per Cent	Monocytes, per Cent
8/27	1,410,000	..	5,050	36	2	59	3
8/29	920,000	..	5,000	68	2	20	10
9/ 2	980,000	..	4,600	67	..	30	3
9/ 8	1,450,000	60	4,200	65	2	29	4
9/12	1,220,000	..	5,600	68	1	27	4
9/20	1,050,000	60	5,700	68	1	29	2
10/ 1	2,800,000	..	5,300	68	1	28	3
10/ 4	2,850,000	..	.....	..	..	..	..
10/10*	2,380,000	..	4,850	65	1	18	6

* It will be noted that the figures in the differential count for this date total only 90 per cent. Because of the international situation it was not possible to check them with the authors before publication of the article.—Editor.

Examination of the peripheral blood by the clinical laboratory of the department of medicine on September 2 revealed the following values: iron 12.5 mg. per hundred cubic centimeters, hemoglobin 3.7 Gm. per hundred cubic centimeters, red cells 1,573,000 per cubic millimeter, volume of cells 12 per cent, platelets 144,327 per cubic millimeter, reticulocytes 6.6 per cent, leukocytes 4,180 per cubic millimeter, mean corpuscular volume 80 cubic microns, mean corpuscular hemoglobin 26.4 micromicrograms, mean corpuscular hemoglobin concentration 30.8 per cent, volume index 0.90, color index 0.91, saturation index 0.96 and icterus index 8 units.

Examination of the peripheral blood by the central laboratory of the Philippine General Hospital on October 2 showed: red cells 2,198,000, hemoglobin 45 per cent, leukocytes 6,575, color index 1.09, neutrophils 58 per cent, lymphocytes 22 per cent, monocytes 2 per cent, transitional cells 2 per cent, eosinophils 13 per cent, basophils 1.67 per cent, premyelocytes 0.33 per cent, staff forms 1 per cent, reticulocytes 2.2 per cent, platelets 358,660, volume of cells 21 per cent, volume index 1.19, mean corpuscular volume 100 cubic microns, mean corpuscular hemoglobin 29.5 micromicrograms and mean corpuscular hemoglobin concentration 29.5 per cent.

On several occasions we ourselves made examinations of the peripheral blood.

On September 8, a differential leukocyte count showed (percentages): basophils 0.8, eosinophils 1.6, myelocytes 0.8, juvenile cells 2.8, staff cells 14, segmented forms 46.4, lymphocytes 29.6, monocytes 3.6 and plasma cells 0.4. The ratio of nucleated red cells to white cells was 9: 250. Definite anisocytosis, poikilocytosis and polychromasia and slight metachromasia were noted, and there was a marked shift to the left.

On September 26 (four days after splenectomy), the red cell count was 1,732,000 and the nucleated cell count (both red and white cells) was 6,700. A differential leukocyte count showed no basophils, 0.4 per cent eosinophils, no myelocytes, 0.8 per cent juvenile forms, 11.6 per cent staff cells, 66 per cent segmented forms, 11.6 per cent lymphocytes, 4.8 per cent monocytes and 0.4 per cent plasma cells. Anisocytosis, poikilocytosis and polychromasia were still pronounced. The ratio of nucleated red cells to white cells was 241: 250 (!). According to this ratio there would be 3,715 white cells and 2,985 nucleated red cells.

On September 27 (five days after splenectomy), the red cell count was 2,440,000, the hemoglobin content 9 Gm. per hundred cubic centimeters and the platelet count 131,760. The percentages of the different types of white cells were as follows: basophils none, eosinophils 1.6, myelocytes and juvenile cells none, staff cells 6.4, segmented forms 68, lymphocytes 23.2, monocytes 0.8 and plasma cells none. The ratio of nucleated red cells to white cells was 38:250 (the day before, 241:250!). The drop in the number of erythroblasts can be explained by the presence of many erythrocytes with Howell-Jolly bodies. The ratio of these erythrocytes with Howell-Jolly bodies to the white cells was 150:100. The increase in the total number of erythrocytes over that on the previous day is noteworthy.

On October 10 (eighteen days after splenectomy), the red cell count was 2,630,000, the hemoglobin content 11 Gm. per hundred cubic centimeters and the white cell count 8,050. The differential count showed (percentages): basophils 0.4, eosinophils 19.6, myelocytes and juvenile forms none, staff cells 4.8, segmented forms 50.4, lymphocytes 19.2, monocytes 5.6 and plasma cells none. There were no more nucleated red cells and no cells with Howell-Jolly bodies. Slight anisocytosis was present.

We also examined the bone marrow on two occasions. On September 5 (before splenectomy), the total cell count was 165,000 per cubic millimeter of bone marrow contents and the differential count (percentages) was as follows[17]:

	E											
B	M	J	St	S	Mgbl	Prom	M	J	St	S	L	Mo	End
0.8	4.8	2.4	2.0	2.0	4.0	10.4	20.4	18.0	14.4	6.3	13.2	0.8	0.4

Normoblasts	185
Basophil erythroblasts	42
Macroblasts	32
Proerythroblasts	30
Megaloblasts	9
Mitotic red cells	18

Ratio.....Nucleated red cells 316 : 250 white cells, or 126.4 nucleated red cells to 100 white cells

On Oct. 6, 1941 (fourteen days after splenectomy), the total cell count was 32,250 per cubic millimeter of bone marrow contents.

	E										
B	M	J	St	S	Mgbl	Prom	M	J	St	S	L	Mo
0.4	0.8	0.8	0.8	5.2	1.2	4.8	16.0	16.4	17.6	24.4	10.4	1.2

Normoblasts	23
Basophil erythroblasts	5
Macroblasts	1

Ratio.....Nucleated red cells 29 : 250 white cells, or 11.6 nucleated red cells to 100 white cells

It is to be added that the result of the fragility test was normal and that repeated examinations of the blood for malarial parasites failed to reveal any. On September 2, the icterus index was 14.5 units; the concentration of bilirubin I was 1.944 mg. per hundred cubic centimeters of serum and that of bilirubin II 0.987 mg.; the van den Bergh reaction was indirect. On October 6, the icterus index was only 3 units, the serum bilirubin 0.18 mg. per hundred cubic centimeters and the van den Bergh reaction delayed direct (very slight).

17. The abbreviations used in these tabulations and in similar ones later in the paper have the following significance: B, basophils; E, eosinophils; M, myelocytes; J, juvenile cells; St, staff cells; S, segmented cells; Mgbl, megaloblasts; Prom, promyelocytes; L, lymphocytes; Mo, monocytes; Mit, mitotic cells; End, endothelial cells.

On October 11, nineteen days after the splenectomy, the patient was discharged recovered.

In this case there were all of the symptoms of constitutional acholuric jaundice. After splenectomy there developed a marked erythroblastosis, which, however, was of short duration. The disappearance of the erythroblastosis was followed by the presence of numerous Howell-Jolly bodies. These bodies also soon disappeared, and a rise in the red cell count was noted. The result of the splenectomy in this case is consistent with the statement given by W. J. Mayo.

We had 2 other cases of splenectomy in childhood for chronic hemolytic anemia in which we made similar observations and obtained the same results after the operation as in the case just cited. The erythroblastosis appeared soon after splenectomy and also rapidly disappeared. It is still a problem whether this erythroblastosis is a constant reaction of the body to splenectomy, but we can at this point surmise that it may occur more frequently than we suppose and that probably it is due to a lack of the inhibitory influence of the spleen on the bone marrow.

In some cases this erythroblastic crisis following splenectomy lasts for a longer time, as in Mediterranean anemia. We have observed 2 such cases.

Case 1.—*History and Course.*—Sofia N., a girl 8 years old, was first admitted to the pediatric service of the Philippine General Hospital on March 13, 1940, because of pallor and general body weakness. Since early in childhood she had been noticed to become gradually but progressively pale. At the age of 4 years she had a disease characterized by fever, jaundice, abdominal pain and vomiting, from which she suffered for about a month. In the last two years she had been having recurrent fever with abdominal pain and occasionally accompanied with cough. For one year before her admission the pallor had become greater and she had complained of a feeling of general body weakness. An enlarging mass at the epigastrium had been noted for four months.

She was underdeveloped and poorly nourished, weighing only 12.4 Kg.; she was very pale and unable to walk. The scleras and the skin were icteric. There was a localized systolic (hemic) murmur at the mitral area. The spleen was enlarged, extending downward to the level of the umbilicus, and was firm. The liver was palpable 2 fingerbreadths below the right subcostal arch. The muscles of the extremities were wasted.

On checking up the condition of health of the family, we found that among five children four were having definite symptoms and hematologic changes of hemolytic anemia. The father, having an increased icterus index and increased bilirubin in the blood, can be considered as the carrier of the disease. Fragility tests of the blood of all of the children with hemolytic anemia gave normal results.

It was suggested to the family that splenectomy be performed on the patient who was hospitalized, but permission was refused. On April 17, 1940, after staying twenty-six days in the ward, she was taken home unimproved. At home she again had abdominal pains and recurrent fever, and in addition edema developed. Because she was becoming worse, she was brought to the hospital for readmission

on October 10. On November 7, in spite of her failure to gain sufficient strength after nearly a month of supportive treatment, she was splenectomized.

The postoperative course was quiet and uneventful. Eleven days after operation the stitches were removed, and the wound healed by primary intention. On December 3, twenty-five days after the operation, the child was discharged able to walk but still pale and without any appreciable gain in weight. At the time of her discharge she weighed only 13 Kg.

Two weeks after discharge she was found to be still noticeably pale, with an ashy color of the skin. There was a slight icteric tinge of the scleras. Nutrition was still poor, but the child was evidently gaining weight, the muscles of the extremities being more developed. She was up and about and was able to sleep and eat well. There was no more fever or abdominal pain.

Four months after the operation her color was better, though not decidedly healthy, and only slight jaundice remained. Her nutrition was greatly improved, and she was much more active, able to play freely with children of her age. Her weight was 16 Kg.

Ten months after the operation the anemia and jaundice were still present.

Laboratory Examinations.—Examination of the peripheral blood by the medical laboratory and by the central laboratory of the Philippine General Hospital gave the following results:

	Medical Laboratory	Central Laboratory	
	3/20/40	3/14/40	10/11/40
Iron, mg. per 100 cc.	15	..	..
Hemoglobin	4.5 Gm.	40%	20%
Red cells	1,510,000	2,300,000	1,190,000
Reticulocytes, per cent	16	31.6	20.3
Volume of cells	13	..	..
Platelets	195,000	160,312	..
White cells	15,700	16,400	17,850
Mean corpuscular volume, cubic microns	86	52	..
Mean corpuscular hemoglobin, micromicrograms	30	..	..
Mean corpuscular hemoglobin concentration, per cent	34	..	..
Volume index	1.02	0.8	..
Color index	1.11	0.6	0.91
Saturation index	1.06	..	..
Hemolysin	None	..	..

Our own examinations of the peripheral blood showed the following values:

Date	B	E	M	J	St	S	L	Mo	Ratio N.R.C. to W.C.	Comments
3/13/40.....	...	2.4	9.6	10.4	8.4	27.2	30.0	1.2	75:250	Anisocytosis, polychromasia and metachromasia
10/11/40.....	..	1.2	1.6	3.6	12.4	46.4	31.6	3.2	36:250	Anisocytosis, polychromasia and metachromasia, poikilocytosis, microcytosis
11/16/40..... (9 days after operation)	2.8	12.0	0.4	0.8	6.0	34.4	36.4	7.2	634:250	Anisocytosis, microcytosis, erythroblastic crisis
11/29/40..... (22 days after operation)	1.2	8.4	2.4	2.4	9.6	40.4	26.4	9.6	2,402:250	Hemoglobin 45%, red cells 1,890,000, nucleated cell count 90,200; therefore, with white cells 8,555, nucleated red cells = 81,645; erythroblastosis, anisocytosis poikilocytosis, polychromasia, marked shift to left, eosinophilia, monocytosis

12/17/40..... (1 mo. 10 days after operation)	...	11.2	0.8	2.0	14.8	30.4	40.4	10.4	6,900:250	Hemoglobin 35%
3/4/41..... (4 mo. after operation)	2.4	15.2	...	0.4	6.0	42.4	32.4	3.2	2,227:250	Red cells 2,888,000, nucleated cells 45,000
4/21/41..... (5 mo. 14 days after operation)	1.2	4.0	...	...	4.0	43.6	46.0	1.2	1,056:250	
9/3/41..... (9 mo. 17 days after operation)	2.0	2.4	2.8	5.2	9.6	32.0	38.8	7.2	1,434:250	Red cells 2,280,000, hemoglobin 40%, reticulocytes 6%, nucleated cell count 119,600; therefore, with white cells 17,629, nucleated red cells = 101,971
11/8/41..... (11 mo. 22 days after operation)	1.6	14.8	0.4	0.8	7.2	35.2	34.4	5.6	1,726:250	Red cells 3,280,000, hemoglobin 50%, nucleated cell count 116,300; therefore, with white cells 16,980, nucleated red cells = 99,320

We made several examinations of the bone marrow.

On March 14 there were pronounced anisocytosis and microcytosis, a shift to the left and erythropoietic hyperactivity.

	E										
B	M	J	St	S	Mgbl	Prom	M	J	St	L	Mo
—	4.4	0.8	0.8	1.2	3.2	8.8	24.8	25.2	13.2	4.4	0.4

Normoblasts	464
Basophil erythroblasts	80
Macroblasts	30
Proerythroblasts	13
Mitotic red cells	5

Ratio.....Nucleated red cells 592 : 250 white cells, or 236.8 nucleated red cells to 100 white cells

On October 14 anisocytosis was still pronounced and there were many basophilic stipplings in the nucleated red cells. Erythropoietic hyperactivity persisted. The total cell count was 145,000 per cubic millimeter of bone marrow contents.

	E												
B	M	J	St	S	Mgbl	Prom	M	J	St	S	L	Mo	Mit	End
—	2.8	0.8	0.8	0.4	3.6	12.8	27.6	23.2	8.8	8.0	8.8	0.8	0.4	1.2

Normoblasts	493
Basophil erythroblasts	47
Macroblasts	22
Proerythroblasts	15
Megaloblasts	11
Mitotic red cells	5

Ratio.....Nucleated red cells 593 : 250 white cells, or 237.2 nucleated red cells to 100 white cells

On November 4 there were few basophilic stipplings and severe anisocytosis, poikilocytosis and metachromasia. The total cell count was 170,000 per cubic millimeter of bone marrow contents.

	E												
B	M	J	St	S	Mgbl	Prom	M	J	St	S	L	Mo	Mit
—	2.0	1.2	1.2	1.6	2.4	10.0	21.2	24.0	16.0	15.2	4.0	0.4	0.8

Normoblasts	340
Basophil erythroblasts	52
Macroblasts	26
Proerythroblasts	18
Megaloblasts	6
Mitotic red cells	5

Ratio.....Nucleated red cells 447 : 250 white cells, or 178.8 nucleated red cells to 100 white cells

On November 23 (sixteen days after operation), the total cell count was 80,500 per cubic millimeter of bone marrow contents.

	E												
B	M	J	St	S	Mgbl	Prom	M	J	St	S	L	Mo	Mit	End
0.4	3.2	0.4	0.8	2.4	4.0	8.4	25.6	18.8	15.6	13.2	5.2	0.4	0.4	1.2

Normoblasts	200
Basophil erythroblasts	19
Macroblasts	11
Proerythroblasts	9
Megaloblasts	3
Mitotic red cells	11

Ratio.....Nucleated red cells 273 : 250 white cells, or 109.2 nucleated red cells to 100 white cells

On Nov. 8, 1941 (eleven months and twenty-two days after operation) the total cell count was 361,600 per cubic millimeter of bone marrow contents.

	E											
B	M	J	St	S	Mgbl	Prom	M	J	St	S	L	Mo
0.4	0.8	2.4	3.2	8.0	2.0	4.8	16.8	16.8	17.2	21.8	5.2	1.6

Normoblasts	2,424
Basophil erythroblasts	90
Macroblasts	39
Proerythroblasts	9
Mitotic red cells	3

Ratio.....Nucleated red cells 2,563 : 250 white cells, or 1,025.2 nucleated red cells to 100 white cells

Our determinations of the icterus index, serum bilirubin and van den Bergh reaction were as follows:

Date	Icterus Index, Units	Serum Bilirubin, Mg./100 Cc.	van den Bergh Reaction
3/19/40	12.7	1.68	Biphasic, delayed
10/11/40	15.9	1.17	Biphasic, prompt
11/19/40	7.2	0.48	Biphasic, delayed
9/ 6/41	15.5	0.82	Biphasic, delayed

We examined both the peripheral blood and the bone marrow for malaria parasites but were unable to find any.

Our examinations of the urine for urobilin, urobilinogen and bilirubin gave the following results.

Date	Urobilin	Urobilinogen	Bilirubin
10/11/40	Trace	Moderate	.....
11/12/40	Trace	.....	None
12/ 2/40	Trace	Slight trace	.....

We examined the feces for urobilin and urobilinogen on two occasions.

Date	Urobilin	Urobilinogen
10/11/40	Fairly heavy	Fairly heavy
11/13/40	Fairly heavy	.....

In this case there were all the evidences of chronic hemolytic anemia with its hemolytic (hemoclastic) crises and signs of increased destruction of red cells. It was of familial occurrence, four of the five children in the family being affected with the disease. In spite of the splenectomy

the symptoms of increased destruction of red cells, such as anemia, jaundice and reticulocytosis, did not disappear. There was, however, no recurrence of the attacks of hemolytic crises. The most striking phenomenon is the extreme erythroblastosis which was noted soon after the splenectomy and persisted unchanged until nearly a year after the operation. Aside from the erythroblastosis, there were many erythrocytes with Howell-Jolly bodies. The anisocytosis seemed to be more severe after than before the splenectomy. The operation did not improve the child's condition to any appreciable degree, and the erythroblastosis that was observed was similar to that which follows splenectomy in cases of Mediterranean anemia.

CASE 2.—*History and Course.*—Lilia A., a girl 6 years old, was admitted to the hospital on Oct. 5, 1940, because of persistent pallor and a mass at the left side of the abdomen.

Since the age of 4 months the child had been noticed to be pale, sickly and susceptible to colds. For the last two years she had had frequent attacks of fever, occurring almost every month and lasting for two to three days, sometimes accompanied by cough. A physician who saw the child informed the parents that the child was anemic and that her spleen and her heart were enlarged. In the fall of 1939 she was admitted to one of the private hospitals of the city because of edema, jaundice and fever.

The father was apparently healthy. The mother's blood showed extreme anisocytosis. A younger (only) brother, 2 years old, had slight anemia and extreme anisocytosis and erythroblastosis (hemolytic anemia).

The child was well developed and well nourished but pale. There was a subicteric tinge of the scleras and of the skin. A hemic murmur was heard over the precordium. The spleen was enlarged to 5 fingerbreadths below the left subcostal arch and extended to the umbilicus on the right.

After the laboratory examinations were completed, a diagnosis of hemolytic anemia was made, and on October 24, nineteen days after the patient's admission, splenectomy was performed. For the first ten days after the operation she had a continuous fever, the temperature reaching 40 C. (104 F.). She was discharged November 21, up and about with the wound completely healed and practically clinically recovered. Two and one-half months after her discharge she was noted to be pale and slightly jaundiced. She was seen several times afterward, and we observed the pallor and the slight jaundice to persist.

Laboratory Examinations.—Examinations of the peripheral blood by the medical laboratory of the department of medicine on October 22 revealed the following values: iron 29.5 mg. per hundred cubic centimeters, hemoglobin 8.8 Gm. per hundred cubic centimeters, red cells 3,010,000, white cells 8,050, platelets 184,320, volume of cells 28 per cent, reticulocytes 4.01 per cent, mean corpuscular volume 93 cubic microns, mean corpuscular hemoglobin 29 micromicrograms, mean corpuscular hemoglobin concentration 31.4 per cent, volume index 1.1, color index 1.07, saturation index 0.98 and icterus index 24 units. On Feb. 26, 1941 (three months after splenectomy) the platelet count was 494,208 and the percentage of reticulocytes 14.5.

The results of our own examinations of the peripheral blood were as follows:

Date	B	E	M	J	St	S	L	Mo	Pl	Ratio N.R.C. to W.C.	Comments
10/6/40.....	...	2.8	—	1.2	3.2	34.0	56.4	1.2	1.2	40:150	Red cells 2,900,000, hemoglobin 47%, nucleated cell count 3,450; anisocytosis, poikilocytosis, polychromasia and metachromasia
10/31/40..... (7 days after operation)	0.4	2.4	—	1.2	18.8	47.6	22.8	4.8	2.0	55:250	Red cells 3,690,000, hemoglobin 50%; pronounced anisocytosis, polychromasia and metachromasia
11/8/40..... (15 days after operation)	2.4	2.4	—	0.8	8.0	35.2	48.0	3.2	...	384:250	Red cells 4,840,000, hemoglobin 60%, nucleated cell count 22,250; therefore, with white cells 15,250, nucleated red cells = 7,000; pronounced anisocytosis and polychromasia
11/18/40..... (25 days after operation)	4.0	5.2	—	0.8	5.6	38.0	42.0	4.0	0.4	1,168:250	
2/1/41..... (3 mo. and 1 wk. after operation)	0.5	5.0	—	...	3.5	43.0	42.0	5.0	1.0	4,770:250	Hemoglobin 60%, severe anisocytosis, polychromasia and fragmentation of red cells
2/25/41..... (4 mo. after operation)	1.6	4.0	—	...	4.0	32.8	35.2	2.4	...	4,800:250	Red cells 3,210,000, nucleated cell count 121,500; pronounced anisocytosis
5/7/41..... (6 mo.after operation)	...	11.2	—	...	3.2	31.6	32.0	2.8	1.2	1,405:250	
8/9/41..... (9 mo. after operation)	2.0	4.0	—	...	3.6	35.6	52.8	1.2	0.8	1,775:250	Red cells 1,955,000, hemoglobin 45%, reticulocytes 2%, nucleated cell count 40,900; pronounced anisocytosis, poikilocytosis, polychromasia and metachromasia
11/8/41..... (11 mo. after operation)	1.2	12.0	—	...	5.6	34.0	44.0	3.2	...	1,062:250	Red cells 3,420,000, hemoglobin 55%, nucleated cell count 81,250; therefore, with white cells 12,593, nucleated red cells = 68,657

We made several examinations of the bone marrow.

On October 8, the total cell count was 260,000 per cubic millimeter of bone marrow contents.

	E											
B	M	J	St	S	Mgbl	Prom	M	J	St	S	L	Mo
0.8	4.8	2.0	1.2	1.2	2.8	5.6	16.8	20.4	18.0	18.0	8.0	0.8

Normoblasts	782
Basophil erythroblasts	113
Macroblasts	44
Proerythroblasts	37
Megaloblasts	9
Mitotic red cells	12

Ratio.....Nucleated red cells 997 : 250 white cells, or 398.8 nucleated red cells to 100 white cells

On November 7 (fourteen days after operation), the total cell count was 115,200 per cubic millimeter of bone marrow contents.

	E												
B	M	J	St	S	Mgbl	Prom	M	J	St	S	L	Mo	Mit
—	0.8	0.8	0.4	—	4.8	12.4	23.6	20.4	11.6	8.8	15.6	0.8	0.8

Normoblasts	190
Basophil erythroblasts	29
Macroblasts	17
Proerythroblasts	8
Mitotic red cells	5

Ratio.....Nucleated red cells 249 : 250 white cells, or 99.6 nucleated red cells to 100 white cells

On November 20 (twenty-seven days after operation), the total cell count was 102,500 per cubic millimeter of bone marrow contents.

	E											
B	M	J	St	S	Mgbl	Prom	M	J	St	S	L	Mo
2.8	4.8	1.6	1.2	2.4	3.6	4.8	12.0	15.6	14.8	13.6	20.4	2.0

Normoblasts	312
Basophil erythroblasts	14
Macroblasts	14
Proerythroblasts	9
Megaloblasts	2
Mitotic red cells	9

Ratio.....Nucleated red cells 365 : 250 white cells, or 146 nucleated red cells to 100 white cells

On Nov. 8, 1941 (eleven months after operation), the total cell count was 71,450 per cubic millimeter of bone marrow contents.

	E												
B	M	J	St	S	Mgbl	Prom	M	J	St	S	L	Mo	End
0.4	0.8	0.4	1.2	5.2	1.2	2.4	7.6	12.4	16.8	24.4	26.4	0.4	0.4

Normoblasts	1,691
Basophil erythroblasts	36
Maeroblasts	8
Proerythroblasts	2
Mitotic red cells	1

Ratio.....Nucleated red cells 1,738 : 250 white cells, or 695.2 nucleated red cells to 100 white cells

We failed to find malaria parasites either in the peripheral blood or in the bone marrow.

The test for fragility of the erythrocytes showed incomplete hemolysis with a concentration of 0.40 per cent (control, 0.40 per cent) and complete hemolysis with a concentration of 0.28 per cent (control, 0.30 per cent).

On Oct. 9, 1940 the icterus index was 16.1 units, the serum bilirubin content 0.96 mg. per hundred cubic centimeters and the van den Bergh reaction biphasic, delayed. On Feb. 26, 1941 the icterus index was 25.7 units, the bilirubin content 2.55 mg. per hundred cubic centimeters and the van den Bergh reaction immediate, direct and moderate.

On Oct. 10, 1940 the urine contained no bilirubin but a trace of urobilin. On March 1, 1941 bilirubin was still absent, but there was a moderate amount both of urobilin and of urobilinogen.

In this case definite improvement followed splenectomy but later there developed an increasing anemia and a constant erythroblastosis. In both of the cases the resting bone marrow which characteristically is present after splenectomy was not observed. By resting bone marrow is meant one showing lowering of the cell count, granulocytopenia, megakaryo-

cytopenia and reduced erythropoietic activity. In both of the cases the cell counts remained high and the erythropoietic hyperactivity was even greater than before the splenectomy. We must emphasize that the failure of the patients to recover cannot be attributed to the presence of accessory spleens, because during the operations a careful search was made for such accessory spleens. In fact, in case 1 two accessory spleens were removed.

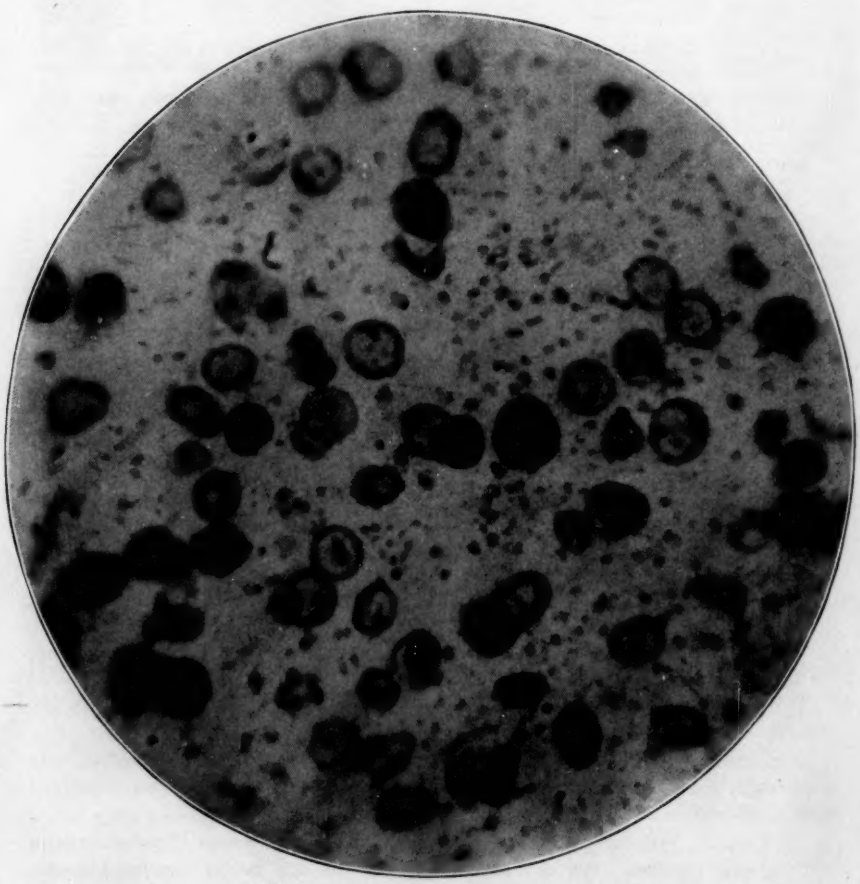

Fig. 1 (case 1).—Peripheral blood, showing 1 segmented cell and 9 erythroblasts. Note the presence of Howell-Jolly bodies.

A comparison of data on the erythroblastosis observed in Mediterranean anemia with our observations showed that the white cell counts obtained in our cases (of hemolytic anemia) after splenectomy were within normal limits, in contrast to high white cell counts in the cases of erythroblastic anemia. The numbers of nucleated red cells were approximately as high in our cases as they were in the cases of Mediterranean anemia.

In the photomicrographs the erythroblastosis and the marked fragmentation and anisocytosis present in both of the cases are shown. The erythroblastosis was of a normoblastic type.

The spleen in each case weighed more than 500 Gm. On histologic section the typical changes of hemolytic anemia were observed. The pulp contained numerous red cells, while the sinuses were empty and

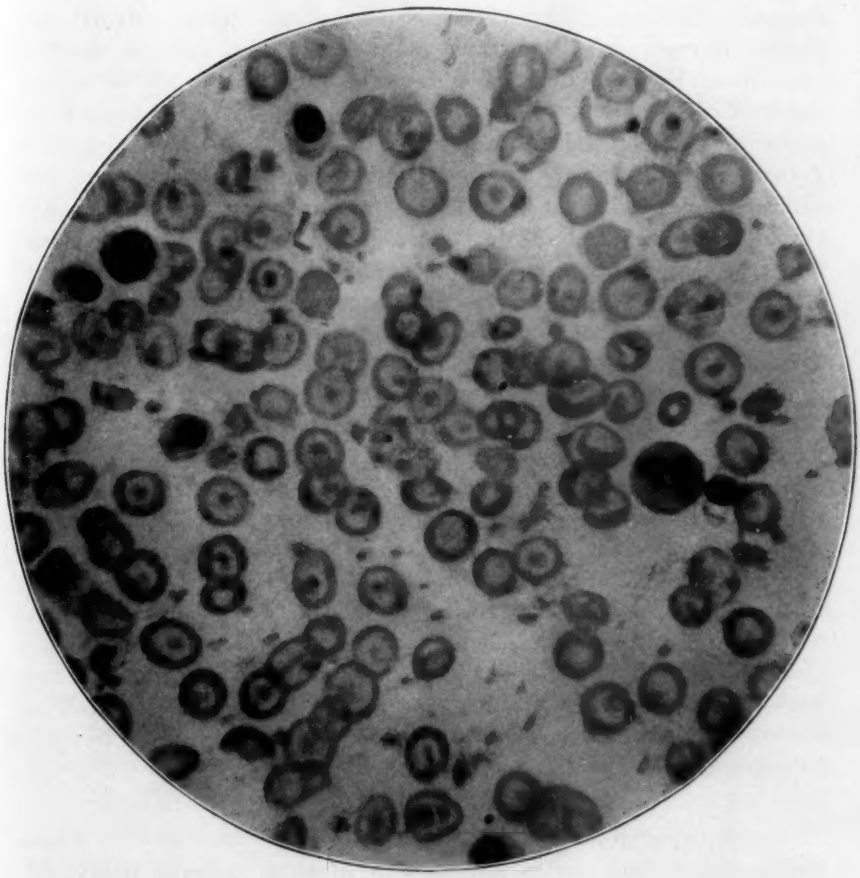

Fig. 2.—Peripheral blood, showing 1 segmented cell, 1 lymphocyte and 4 erythroblasts.

nearly collapsed. The walls of the sinuses were composed of cells with large nuclei and scanty cytoplasm. The follicles were atrophied, and there was hemosiderosis of the reticulum cells of the spleen. There were no erythropoietic foci, hemorrhages or infarcts, which are present in sickle cell anemia.

The question of whether the erythroblastosis that occurs after splenectomy is due to a peculiar type of anemia of racial character, like the Medi-

terranean anemia of the Italians and Greeks or like the sickle cell anemia of Negroes, is difficult to answer. Our patients were Filipino children. Moreover, our cases furnish no evidence as to whether the erythroblastosis following splenectomy is due to an abnormal function of the bone marrow, as that in Mediterranean anemia is supposed to be. In cases of Mediterranean anemia symptoms of faulty function of the bone marrow are evident. The fact that erythroblastosis of short duration is a frequent response after splenectomy in cases of hemolytic anemia, although not present in every case, is in favor of the supposition that the erythroblastosis of longer duration is due to the presence or lack of certain factors that produce temporary erythroblastosis. It is of importance to know how long the erythroblastosis will last. We have presented 2 cases in which nearly one year after splenectomy there were still persistent anemia, jaundice, reticulocytosis and increased urobilinogen output, indicating that the hemolytic disease had not abated. While it is true that there were no more attacks of hemolytic or hemoclastic crises, the disease and the anemia remained practically unchanged. The practical question would be which patients with chronic hemolytic anemia would be subjected to splenectomy or would respond favorably to the operation. We are not in a position at the present time to make any definite statement or answer. We have, however, observed that the effects of splenectomy do not depend on the presence or absence of spherocytosis or on the presence or absence of increased fragility of the red cells. In both of our cases these conditions are absent. On the other hand, we observed other cases in which both spherocytosis and increased fragility of the red cells were absent but there was a remarkable recovery after splenectomy. We can agree with Thompson [2] that hemolytic anemia cannot be considered from the viewpoint of an etiologic entity. The classification into a typical and an atypical variety likewise cannot be considered satisfactory, and further studies must be made so that the indications for splenectomy and for other treatment can be made more precise.

SUMMARY

Transitory erythroblastosis frequently follows splenectomy for hemolytic anemia. One case is discussed in which a pronounced erythroblastosis disappeared within a few days.

Two cases of erythroblastosis following splenectomy for chronic hemolytic anemia in children are presented. There were persistent anemia, jaundice and all the symptoms of increased destruction of red cells in spite of splenectomy.

The erythroblastosis following splenectomy in cases of hemolytic anemia is compared with that following splenectomy in cases of Mediterranean anemia.

The possible causes of the erythroblastosis and of the lack of improvement after splenectomy in cases of hemolytic anemia are discussed.

A STUDY OF PERTUSSIS ANTIBODIES

PROTECTIVE, AGGLUTINATING AND COMPLEMENT-FIXING ANTIBODIES IN PATIENTS WITH PERTUSSIS, PERSONS EXPOSED TO PERTUSSIS AND PERSONS WITH NO KNOWN EXPOSURE

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We reported in a previous paper [1a] that protective antibodies were found in a large percentage of patients with pertussis who whooped three weeks or longer and that these antibodies were found only occasionally earlier in the disease. Agglutinins were found at that time in less than one half of the patients tested, and the agglutinin titers of these patients did not correspond either to the duration of the illness or to the protective antibody titers of their serums.

In continuation of these studies, it seemed important to determine: (1) whether pertussis-protective, agglutinating and complement-fixing antibodies are present in persons with no history of pertussis and no symptoms of illness; (2) whether the aforementioned antibodies are found late in the course of pertussis as well as during the early stage; (3) whether these antibodies are stimulated in persons who are intimately exposed to persons with active pertussis but do not acquire clinically typical pertussis, and (4) whether these antibodies are found in persons who have coughs and colds but who have had no known exposure to pertussis.

An opportunity to carry out this investigation was given at Letchworth Village, a state institution for the mentally defective. This institution has a population of approximately 3,800 patients, of all ages,

From the Bureau of Laboratories, New York City Department of Health.

1. (*a*) Mishulow, L.; Klein, I. F.; Liss, M. M., and Leifer, L.: J. Immunol. **37**:17, 1939. (*b*) Mishulow, L.; Wilkes, E. T.; Liss, M. M.; Lewis, E.; Berkey, S. R., and Leifer, L.: Stimulation of Pertussis Protective Bodies by Vaccination: A Comparative Study of Protective, Agglutinating and Complement-Fixing Antibodies, Am. J. Dis. Child. **62**:1205 (Dec.) 1941.

both male and female. The patients are housed in separate cottages, each of which contains 85 to 130 patients, depending on its size.

The patients are grouped into six major groups, according to sex, infirmity, chronologic age and mental age. Each of these groups has from four to eight cottages and functions as an independent unit. Each major group has a school, a service building with kitchen and dining room and a hall that is used as a gymnasium and for dances and entertainments. Thus the patients in each major group are in close contact not only in the cottages but in the dining rooms and in the entertainment hall and in some instances in school. There is comparatively little contact between the different major groups except at weekly showings of motion pictures, church, Sunday school, athletic games and occasional holiday celebrations, where the major groups of the same sex intermingle. One major group of patients, who are of very low mentality, are segregated from the other major groups and are permanently confined to their cottages. These patients have no contact with the other patients in the institution. Records are kept of illnesses that occur during the patient's residence at the institution. Since 1937, authentic histories have been available of the time of occurrence of pertussis infection at the institution and of the persons who were exposed to patients with active pertussis.

EXPERIMENTS

We began this investigation in November 1939, when there had been no pertussis infection at the institution for some time. This enabled us to obtain serums from physically healthy persons who had no history of pertussis before admission and no known exposure to this disease at the institution. The tests were carried out as follows:

EXPERIMENT 1.—*Protective, agglutinating and complement-fixing antibodies in children and adults who had no history of pertussis.*

Serums were obtained from 72 persons of both sexes whose ages ranged from 8 to 60 years. They may be divided according to their ages into three groups as follows: group 1, 25 persons 8 to 19 years of age; group 2, 32 persons 20 to 37 years of age, and group 3, 15 persons 40 to 60 years of age. This gave us a representative sample of the physically normal population at the institution.

Owing to the illness of one of the authors (L. M.), these serums could not be tested at the time they were obtained. They were stored at 8 to 10 C. until December 1940, when the studies were resumed. Each serum was then tested for protective, agglutinating and complement-fixing antibodies. The methods of testing for these antibodies have been described in our previous publications.[1b]

In charting the results obtained in testing for protective antibodies, the result was considered positive when 0.2 cc. protected 30 per cent or more of eight to ten mice tested. A survival of less than 30 per cent of the mice was considered a negative result, since occasionally one or two mice survived the test doses of the culture when no serum was given. The result of agglutination was recorded in terms of the highest dilution of the serum that showed distinctly visible clumps. Indistinct or no agglutination in a 1:10 dilution of the serum was recorded as negative.

Complement fixation was recorded in terms of the smallest amount of undiluted serum that gave complete fixation when incubated for one hour at 37 C. after the sensitized cells were added. The largest amount of serum tested was 0.02 cc. Incomplete or no fixation in this amount was considered negative.

The results obtained in this experiment are given in table 1. This table shows that of 72 physically well persons with no history of pertussis, 11, or 15.2 per cent, had protective antibodies in their serums. Four persons in this group had agglutinating antibodies, but only 1 of these 4 had protective antibodies in addition. No complement-fixing antibodies were found in any of them. The presence of protective antibodies in persons with no history of pertussis could not be attributed to acquired immunity due to age, because persons with and without protective antibodies were found in all the age groups tested.

TABLE 1.—*Pertussis Antibodies in Persons Without Illness and Without a History of Pertussis*

Persons Tested	Age, Years	Results *			
		Number	Aggl.	C. - F.	Mouse Protection, Percentage Survived
72	13 to 56	10	0	0	30 to 70
	48	1	60	0	44
	19 to 37	3	30 to 50	0	0
	8 to 60	58	0	0	0
Protective antibodies in 11 persons..... 15.2%					
Agglutinating antibodies in 4 persons..... 5.5%					

* Aggl. 0 indicates incomplete or no agglutination in a 1:10 dilution of the serum; C.-F. 0, incomplete or no complement fixation in 0.02 cc. of the serum; protection 0, survival of none or of less than 30 per cent of eight to ten mice for one week.

N. B. The numbers under "Aggl." represent the titer of the serums.

EXPERIMENT 2.—*Protective, agglutinating and complement-fixing antibodies in patients with clinically typical pertussis and in persons intimately exposed to them.*

During November and December 1940 and January 1941 there was an outbreak of pertussis in some of the cottages at the institution. This gave us an opportunity to study the development of protective, agglutinating and complement-fixing antibodies in patients with pertussis and in persons who had been in contact with them.

Thirty serums were obtained from 25 patients with pertussis in seven cottages, and 21 serums from 21 persons who resided in those cottages and were intimately and repeatedly exposed to the patients with active infection. In addition, 32 serums were obtained from 26 persons who were in the major group with the patients with pertussis and were repeatedly exposed to them in the dining room, on the playground and in the entertainment hall and in some instances also in school.

The results obtained in testing these serums are given in tables 2, 3 and 4.

Table 2 shows that 22, or 88 per cent, of the 25 patients with pertussis had protective antibodies, 3 patients had agglutinins and 2 had complement-fixing antibodies. Two patients in this group were tested during the first week of illness, and both of them had negative reactions for all three antibodies at that time. When they were retested one month after

TABLE 2.—*Pertussis Antibodies in Twenty-Five Patients with Clinically Typical Pertussis*

Serial Number	Age, Years	Onset	Bled	Result			
						Mouse Protection	
				Aggl.	C. - F.	Number Survived	Per Cent
1	11	10/20/40	11/ 6/40	0	0.008	6/7	85.7
			12/ 5/40	0	0	4/10	40
2	5	10/23/40	11/ 7/40	0	0	3/5	60
			12/ 5/40	0	0	1/5	20
3	7	11/ 1/40	11/ 7/40	0	0	0/4	0
			12/ 5/40	0	0	1/3	?
4	6	10/30/40	11/ 7/40	0	0	0/2	0
			12/ 5/40	0	0.008	2/5	40
5	13	12/ 8/40	12/27/40	0	0	0/8	0
6	8	11/20/40	12/20/40	0	0	1/8	0
7	28	12/ 7/40	1/ 3/41	0	0	3/8	37.5
			4/ 1/41	0	0	8/10	80
8	15	11/11/40	4/ 1/41	0	0	10/10	100
9	19	11/23/40	4/ 1/41	0	0	8/10	80
10	32	11/30/40	4/ 1/41	400	0	10/10	100
11	15	12/ 7/40	4/ 1/41	10	0	10/10	100
12	15	12/ 7/40	4/ 1/41	0	0	6/10	60
13	10	12/13/40	4/ 1/41	0	0	6/10	60
14	33	12/27/40	4/ 1/41	0	0	8/10	80
15	46	12/ 8/40	4/ 1/41	0	0	7/10	70
16	18	12/ 8/40	4/ 1/41	0	0	9/10	90
17	22	12/ 2/40	4/ 1/41	10	0	7/10	70
18	17	12/ 2/40	4/ 1/41	0	0	7/10	70
19	9	11/24/40	4/ 1/41	0	0	9/10	90
20	8	11/13/40	4/ 1/41	0	0	9/10	90
21	10	10/28/40	4/ 1/41	0	0	5/8	62.5
22	15	11/25/40	4/ 1/41	0	0	4/9	44.4
23	12	11/25/40	4/ 1/41	0	0	6/7	85.7
24	10	10/24/40	4/ 1/41	0	0	9/9	100
25	16	11/15/40	4/ 1/41	0	0	8/9	88.8

Tests made on 25 subjects, 30 serums

Protective antibodies in 22 persons	88%
Agglutinating antibodies in 3 persons	12%
Complement-fixing antibodies in 2 persons	8%

the onset of the disease, 1 of them had protective and complement-fixing antibodies but the serum of the other still gave negative reactions. Five patients were tested two to four weeks after the onset of the whoop; 3 of them had protective antibodies, but only 1 of these 3 had complement-fixing antibodies and none of them had any agglutinins. Thus 4 of the 7 patients who were tested within two to four weeks after the onset of the disease had protective antibodies. Nineteen patients were tested

four to five and a half months after the onset of the disease. All of them had protective antibodies, and most of them had these antibodies in high

TABLE 3.—*Pertussis Antibodies in Persons Residing in Cottages in Which There Were Patients with Active Pertussis*

				Result				Exposed to Pertussis in Cottages		
						Mouse Protection				
Age, Yr.	Illness	Onset	Bled	Aggl.	C. - F.	Number Survived	Per Cent	Cottage	No. Cases	Date of Onset of First and Last Illness
22	Head cold	1/15/41	1/18/41	0	0	0/9	0			
24	Head cold	1/15/41	1/18/41	0	0	5/10	50			
28	Head cold	1/15/41	1/18/41	0	0	1/10	0			
27	Head cold	1/15/41	1/18/41	0	0	4/7	57.1			
28	Head cold	1/15/41	1/18/41	0	0	1/9	0			
25	Head cold	1/15/41	1/18/41	0	0	8/9	88.8	Delta	5	11/11/40-12/13/40
36	Head cold	1/15/41	1/31/41	75	0	9/10	90			
16	Head cold	1/15/41	2/10/41	2,400	0.006	9/9	100			
23	Head cold	1/15/41	1/18/41	0	0	2/10	20			
15	Head cold	1/15/41	1/18/41	0	0	2/10	20			
33	Head cold	1/15/41	2/ 5/41	50	0.02	8/10	80			
29	No illness	.....	4/ 1/41	0	0	6/10	60			
13	Head cold	1/14/41	1/18/41	0	0	8/10	80			
15	Head cold	1/14/41	1/18/41	150	0	7/10	70	Theta	10	11/11/40-12/13/40
13	Head cold	1/14/41	1/18/41	0	0	3/10	30			
13	Cough and fever	12/26/40	12/27/40	0	0	0/9	0			
15	No illness	.....	1/22/41	0	0	2/10	20	D	1	11/17/40
12	Head cold, cough	12/20/40	1/ 8/41	0	0	0/8	0			
10	Head cold, cough	12/20/40	12/20/40	0	0	4/9	44.4	S	11	8/30/40-10/20/40
14	No illness	.....	4/ 1/41	10	0	2/9	22.2	F	2	11/15/40-11/22/40
11*	Head cold	12/20/40	1/ 8/41	0	0	0/7	0	X	12	11/ 1/40-11/22/40

Tests made on 21 subjects, 21 serums
Protective antibodies in 11 persons..... 52%
Agglutinating antibodies in 5 persons..... 23.8%
Complement-fixing antibodies in 2 persons..... 9.5%

* Had whooping cough before admission

titer. Only 3 of these patients had agglutinins, and only 1 of these 3 had a high titer of these antibodies. None of the patients in this group had any complement-fixing antibodies. The 3 patients in this group who

did not have protective antibodies were tested nineteen days, one month and one month respectively after the onset of the disease. Possibly later in the disease their serums might have been found to contain the antibodies.

TABLE 4.—*Pertussis Antibodies in Persons Who Were Exposed to Patients with Active Pertussis in the Dining Room, at Motion Picture Showings and on the Playground*

No.	Age, Years	Illness	Onset	Bled	Result: Agglutination	Result: Complement-Fixation	Result: Mouse Protection: Number Survived	Result: Mouse Protection: Per Cent
1	12	Sore throat and cough..	11/18/40	12/12/40	0	0	0/6	0
2	16	Sore throat and cough..	11/18/40	12/13/40	0	0	5/7	71
3	14	Cough	12/20/40	1/22/41	0	0	4/10	40
4	19	Cough	12/22/40	1/22/41	0	0	0/10	0
5	16	Cough	12/26/40	1/ 8/41	0	0	0/10	0
6	14	Running nose	12/31/40	1/22/41	0	0	0/9	0
7	15	Running nose	12/31/40	1/ 8/41	0	0	6/10	60
				1/22/41	0	0	9/10	90
8	14	Running nose	1/ 3/41	1/ 8/41	0	0	2/10	20
				1/22/41	0	0	0/10	0
9	15	Cough	12/20/40	1/ 8/41	0	0	4/10	40
				1/24/41	0	0	4/10	40
10	13	Cough	12/20/40	1/ 4/41	0	0.009	9/10	90
				1/22/41	0	0.02	3/7	42.8
11	14	Cough	12/31/40	1/ 8/41	0	0	5/7	71
				1/22/41	10	0	5/9	55.5
12	16	Cough	12/20/40	1/22/41	0	0	2/10	20
13	18	Running nose	12/31/40	1/22/41	0	0	4/10	40
14	16	Cough	12/20/40	1/22/41	0	0	2/8	25
15	15	Cough	12/20/40	1/ 8/41	0	0	0/10	0
				1/22/41	0	0	5/9	55.5
16	14	Sore throat and cough..	12/31/40	1/22/41	25	0	4/9	44.4
17	21	Cold	1/ 8/41	1/22/41	0	0	0/10	0
18	19	Head cold	1/14/41	1/18/41	0	0	0/10	0
19	16	Head cold	1/14/41	1/18/41	0	0	0/10	0
20	12	Head cold	1/ 2/41	1/ 8/41	0	0	2/10	20
21	32	Head cold	1/14/41	1/31/41	0	0	0/10	0
22	39	Cold	1/14/41	1/31/41	37.5	0	6/10	60
23	..	Cough	1/18/41	1/18/41	0	0	5/10	50
24	17	Cold and cough	1/12/41	1/31/41	0	0	8/10	80
25	14	No illness	.....	4/ 1/41	0	0	0/10	0
26	15	No illness	.....	4/ 1/41	0	0	7/10	70

Tests made on 26 subjects, 32 serums
Protective antibodies in 13 persons 50%
Agglutinating antibodies in 3 persons 11.5%
Complement-fixing antibodies in 1 person 3.8%

Table 3 shows that 11, or 52 per cent, of the 21 persons who were intimately exposed to patients with active pertussis in the cottages where they resided had protective antibodies of a significant titer. Sixteen persons in this group had head colds four to five weeks after the first attack of pertussis in their cottages, and 2 more had colds after two months. Ten of the 18 patients who had colds after exposure to patients

with pertussis had protective antibodies. Two of the patients who had protective antibodies also had agglutinins and complement-fixing antibodies, and 2 more had agglutinins but no complement-fixing antibodies. One patient had a cough and fever five weeks after exposure, but his serum gave negative reactions for all three antibodies. Three persons in this group remained well. One of these 3 was tested four months after exposure and was found to have protective antibodies but no agglutinins or complement-fixing antibodies. The other 2 were tested two and four and a half months respectively after exposure. Neither of them had protective or complement-fixing antibodies; 1 had agglutinins of a low titer and the other had none.

Table 4 shows that of the 26 persons who were in the same major group with the patients with pertussis and were repeatedly exposed to the patients in the dining room, on the playground and in the entertainment hall and in some cases also in school, 13, or 50 per cent, had protective antibodies, 3 had agglutinins and 1 had complement-fixing antibodies. Twenty-four persons in this group had head colds or coughs at the time that specimens of their blood were obtained for the test, and 2 were well. One of the 2 persons who were well had a high titer of protective antibodies, and the other did not have any of these antibodies. Neither of them had agglutinins or complement-fixing antibodies. Thus the results in this group correspond closely to those that we obtained in the group that resided in the infected cottages in which there were persons with the infection. The results in these two groups show that protective antibodies were present in approximately 51 per cent of the persons in whom a mild infection of the respiratory tract developed after exposure to pertussis and in some of those who did not have any illness.

EXPERIMENT 3.—*Protective, agglutinating and complement-fixing antibodies in persons who were in major groups that had no patients with pertussis but mingled occasionally with the groups that had such patients.*

Seventy-six serums were obtained from 55 persons in major groups in which there was no pertussis but which came in contact with other major groups at motion picture showings, church, Sunday school, athletic games and holiday celebration. Some of them therefore might have come in contact with patients with pertussis who were without typical symptoms of pertussis at the time.

The results of this experiment are given in table 5. This table shows that 10, or 18.1 per cent, of the 55 persons tested had protective antibodies; 8 (14.5 per cent) had agglutinins, but in 4 of these 8 the titer was very low. None of them had any complement-fixing antibodies.

Forty-four persons in this group had head colds or coughs or both; 6 had sore throats; 2 had a history of headache one to two weeks

TABLE 5.—*Pertussis Antibodies in Persons in Major Groups That Had No Patients with Pertussis but had Contact with the Groups That Had Such Patients*

No.	Age, Years	Illness	Onset	Bled	Result			
							Mouse Protection	
					Aggl.	C.-F.	Number Survived	Per Cent
1	29	Head cold, cough.....	12/31/40	1/ 4/41	0	0	0/3	0
				1/17/41	0	0	3/4	75
2	53	Head cold.....	1/ 3/41	1/17/41	0	0	0/3	0
3	32	Head cold.....	1/ 3/41	1/ 4/41	0	0	0/3	0
				1/17/41	0	0	0/2	0
4	41	Sore throat, head cold, cough	1/ 1/41	1/17/41	0	0	0/4	0
5	31	Cough.....	1/ 1/41	1/ 4/41	0	0	0/2	0
6	62	Head cold, cough.....	1/ 4/41	1/17/41	0	0	0/3	0
7	42	Head cold, cough.....	1/ 2/41	1/ 4/41	0	0	1/3	?
				1/17/41	0	0	0/4	0
8	14	Head cold, cough.....	12/28/40	1/ 4/41	0	0	0/8	0
				1/17/41	0	0	0/9	0
9	30	Head cold, cough.....	12/30/40	1/ 4/41	0	0	0/10	0
				1/17/41	0	0	0/10	0
10	41	Head cold.....	1/ 3/41	1/ 4/41	75	0	3/7	42.8
				1/17/41	50	0	7/10	70
11	23	Head cold, cough.....	1/ 3/41	1/ 4/41	50	0	1/10	0
				1/17/41	17.5	0	5/9	55.5
12	22	Head cold.....	1/ 4/41	1/ 4/41	0	0	0/7	0
13	19	Head cold, cough.....	1/ 3/41	1/ 4/41	0	0	0/10	0
				1/17/41	0	0	4/9	44.4
14	19	Head cold, cough.....	12/30/40	1/17/41	0	0	0/10	0
15	25	Head cold.....	1/17/41	1/17/41	0	0	0/7	0
				1/31/41	0	0	0/9	0
16	15	Head cold.....	1/14/41	1/17/41	0	0	0/10	0
				1/31/41	0	0	0/10	0
17	31	Cough.....	1/ 2/41	1/ 4/41	0	0	0/6	0
				1/17/41	0	0	0/9	0
18	23	Cold.....	12/30/40	1/ 4/41	0	0	1/8	0
				1/17/41	0	0	9/10	90*
19	34	Cold.....	12/30/40	1/ 8/41	0	0	1/8	0
20	43	Head cold.....	1/ 1/41	1/17/41	0	0	2/10	20
21	36	Cough.....	12/30/40	1/24/41	0	0	1/9	0
22	25	Head cold.....	12/31/40	1/ 4/41	17.5	0	1/8	0
				1/18/41	0	0	1/6	0
23	30	Cough.....	1/ 2/41	1/22/41	0	0	2/10	20
24	16	Cough.....	1/ 3/41	1/22/41	0	0	0/9	0
25	22	Cough and sore throat..	1/ 3/41	1/22/41	0	0	2/10	20
26	21	Cough.....	1/ 4/41	1/ 8/41	0	0	2/10	20
				1/22/41	0	0	3/10	30
27	20	Head cold.....	1/ 5/41	1/22/41	0	0	1/10	0
28	30	Sore throat and cough..	12/31/40	1/22/41	0	0	1/9	0
29	27	Cough.....	1/ 5/41	1/22/41	10	0	0/10	0
30	18	Cough, running nose....	1/ 2/41	1/22/41	0	0	0/9	0
31	20	Head cold.....	1/16/41	1/17/41	0	0	0/9	0
32	38	Cold and cough.....	11/22/40	12/20/40	0	0	0/7	0
33	19	Cold and cough.....	11/22/40	12/13/40	0	0	1/7	0
34	32	Head cold.....	12/27/40	12/27/40	0	0	3/9	33.3
				1/ 8/41	0	0	4/10	40
35	22	Head cold, sore throat..	12/26/40	1/ 8/41	0	0	1/8	0
36	28	Cold.....	12/29/40	1/17/41	0	0	0/9	0
37	22	Cold.†.....	12/29/40	1/17/41	17.5	0	6/10	60
38	23	Head cold.....	12/30/40	1/17/41	0	0	0/10	0
39	48	Cold.....	12/30/40	1/17/41	0	0	0/10	0
40	20	Headache.....	12/31/40	1/17/41	0	0	1/10	0
41	21	Sore throat and cough..	11/18/40	12/13/40	25	0	2/7	28.5
42	23	Headache.....	12/27/40	1/ 8/41	0	0	1/8	0
43	33	Headache and earache..	1/ 8/41	1/ 8/41	0	0	2/10	20
				1/22/41	0	0	5/9	55.5

TABLE 5.—*Pertussis Antibodies in Persons in Major Groups That Had No Patients with Pertussis But Had Contact with the Groups That Had Such Patients—Continued*

No.	Age, Years	Illness	Onset	Bled	Result: Agglutination	Result: Complement-Fixation	Result: Mouse Protection: Number Survived	Result: Mouse Protection: Per Cent
44	43	Cold in the chest.....	12/30/40	1/ 4/41	0	0	3/6	50
				1/17/41	37.5	0	6/10	60
45	42	Head cold.....	12/30/40	1/ 4/41	0	0	0/10	0
				1/17/41	0	0	1/10	0
46	18	Head cold †.....	12/30/40	1/ 4/41	0	0	0/9	0
				1/17/41	0	0	0/9	0
47	30	Head cold, sore throat..	1/ 8/41	1/22/41	0	0	0/8	0
48	29	Sore throat.....	12/26/40	1/ 4/41	0	0	0/3	0
				1/17/41	0	0	0/7	0
49	36	Sore throat.....	1/ 3/41	1/ 4/41	0	0	0/8	0
				1/17/41	0	0	0/8	0
50	19	Sore throat †.....	1/ 3/41	1/17/41	0	0	0/10	0
51	31	Sore throat.....	12/ 1/40	1/17/41	0	0	0/9	0
52	44	Sore throat.....	12/27/40	1/ 8/41	0	0	2/8	25
53	24	Sore throat.....	12/30/40	1/24/41	0	0	0/10	0
54	43	No illness.....	.....	12/ 7/40	0	0	0/6	0
55	25	No illness.....	.....	12/ 7/40	10	0	2/8	25

Tests made on 55 subjects, 76 serums

Protective antibodies in 10 persons	18.1%
Agglutinating antibodies in 8 persons	14.5%
Complement-fixing antibodies in no persons	0%

* Tested against 250,000,000 bacteria only.
† Had whooping cough before admission.

previously; 1 had a headache and earache, and 2 were well. Of the 44 persons who had head colds or coughs, 9 had protective antibodies. Among these 9 there was 1 patient who had a history of pertussis before his admission to the institution, two years previously. But there was another patient in this group who had a history of pertussis before his admission, one and a half years previously, and his serum contained none of the three antibodies.

The 6 patients who had sore throats had no pertussis antibodies, although 1 of them had a history of pertussis three years previously. The 2 patients who had had headaches one to two weeks previously had no antibodies. The patient who had a headache and earache on the day of the first test had no antibodies, but when he was tested two weeks later he had protective antibodies. The 2 persons who were well had no protective or complement-fixing antibodies, but 1 of them had agglutinins of low titer.

Twenty of the patients who had colds or coughs were tested within a few days of the onset of the illness, and 3 of them were found to have protective antibodies. When they were retested two weeks later, the 3 whose serums had contained the antibodies had an increased titer and 6 of those who had had negative reactions were found to have antibodies.

EXPERIMENT 4.—*Protective, agglutinating and complement-fixing antibodies in persons with colds who had no known exposure to pertussis.*

Forty-one serums were obtained from 30 persons who resided in three cottages which were segregated so that the inmates had no contact with those of the other

TABLE 6.—*Pertussis Antibodies in Persons with Colds Who Were Housed in Segregated Cottages and Had No Known Exposure to Pertussis*

No.	Age, Years	Illness	Onset	Bled	Result		Mouse Protection	
					Aggl.	C.-F.	Number Survived	Per Cent
1	6	Head cold and cough....	11/ 5/40	11/ 6/40	0	0	0/3	0
				12/ 5/40	0	0	0/8	0
2	6	Head cold and cough....	11/ 5/40	11/ 6/40	0	0	0/3	0
3	11	Head cold and cough....	11/ 5/40	11/ 6/40	0	0	0/4	0
				12/ 5/40	0	0	0/5	0
4	6	Head cold and cough....	11/ 5/40	11/ 6/40	37.5	0	0.5	0
5	6	Head cold and cough....	11/ 5/40	11/ 6/40	0	0	0/3	0
				12/ 5/40	0	0	1/8	0
6	6	Head cold and cough....	11/ 5/40	11/ 6/40	0	0	0/3	0
				12/ 5/40	0	0	0/3	0
7	62	Head cold and cough....	11/ 5/40	11/ 6/40	0	0	0/5	0
				12/ 5/40	0	0	1/5	0
8	8	Head cold and cough....	11/ 5/40	11/ 6/40	0	0	0/4	0
				12/ 5/40	0	0	0/4	0
9	3	Head cold and cough....	11/ 5/40	11/ 6/40	0	0	0/5	0
10	10	Head cold and cough....	11/ 6/40	12/ 5/40	0	0	0/5	0
11	6	Head cold and cough....	11/ 5/40	12/ 5/40	0	0	1/5	?
12	7	Head cold and cough....	11/ 5/40	11/ 6/40	0	0	0/3	0
				12/ 5/40	0	0	1/3	0
13	10	Head cold and cough....	11/ 5/40	11/ 7/40	0	0	0/8	0
				12/ 5/40	0	0	0/5	0
14	7	Head cold.....	1/1 5/40	11/ 7/40	0	0	0/4	0
15	23	Head cold.....	1/14/41	1/31/41	0	0	0/10	0
16	6	Head cold.....	1/16/41	2/ 5/41	0	0	0/9	0
17	11	Head cold.....	1/16/41	1/18/41	0	0	0/10	0
18	12	Head cold.....	1/16/41	2/ 5/41	0	0	0/10	0
19	12	Head cold.....	1/16/41	1/18/41	0	0	0/10	0
20	14	Head cold.....	1/16/41	2/ 5/41	0	0	0/10	0
21	15	Head cold.....	1/16/41	2/ 5/41	0	0	3/10	30
22	7	Head cold.....	1/16/41	2/ 5/41	0	0.02	4/10	40
23	13	Head cold.....	1/16/41	2/ 5/41	0	0	0/10	0
24	15	Cold.....	1/17/41	2/ 3/41	0	0	0/8	0
25	23	Cold.....	1/ 3/41	1/17/41	0	0	0/10	0
				2/ 3/41	0	0	0/10	0
26	31	Cold.....	1/ 8/41	2/ 3/41	0	0	1/9	0
27	20	Head cold.....	1/ 9/41	1/31/41	0	0	0/9	0
				3/ 3/41	0	0	1/9	0
28	25	Head cold.....	1/ 9/41	1/17/41	0	0	0/8	0
				1/31/41	0	0	0/10	0
29	14	Head cold.....	1/ 9/41	1/31/41	0	0	0/10	0
30	12	Head cold.....	1/11/41	1/31/41	0	0	3/10	30

Tests made on 30 subjects, 41 serums
Protective antibodies in 3 persons..... 10%
Agglutinating antibodies in 1 person..... 3.3%
Complement-fixing antibodies in 1 person..... 3.3%

cottages. All of the 30 persons in this group had head colds at the time of the test, and none of them had a history of pertussis.

The results of this experiment are given in table 6. Protective antibodies were found in 3, or 10 per cent, of these patients. Agglutinins

were found in 1 patient. Complement-fixing antibodies were found in 1 of the patients who had protective antibodies.

SUMMARY AND COMMENT

An investigation was carried out at an institution for the mentally defective to determine the presence of pertussis-protective, agglutinating and complement-fixing antibodies in physically healthy children and adults who had no history of pertussis and no known recent exposure to this disease; in patients with clinically typical pertussis; in persons who were exposed to patients with active pertussis but in whom the typical symptoms of the disease did not develop, and in patients who had colds and coughs but no known exposure to pertussis. A total of 272 serums from 229 persons were tested.

A group of 72 persons with no history of pertussis were tested. Among them were included males and females between 8 and 60 years of age. This gave us a group that was representative of the general population at the institution. All of them were physically well at the time of the test. Eleven persons in this group, or 15.2 per cent, had pertussis-protective antibodies, and 4 persons (5.5 per cent) had agglutinins, but only 1 of these 4 had both protective and agglutinating antibodies. None of them had complement-fixing antibodies. The presence of protective antibodies in persons who were said to have had no previous pertussis infection could not be attributed to immunity that is acquired with age, since persons with and without protective antibodies were found in all the age groups tested. There is a possibility that some of them were exposed to visiting relatives or friends who had the infection but that the infective doses were too small to produce clinical symptoms of pertussis. It is also possible that their histories of "no previous infection" were incorrect. Whatever the explanation may be, the fact that 15.2 per cent of the physically normal population had protective antibodies seems to us rather significant, as it may explain the reason for the resistance of a considerable percentage of presumably nonimmune persons when they are exposed to patients with active pertussis. There is no reason to assume that we were dealing with a specially immune group at the institution or that mentally defective persons differ in this respect from the average normal population of a city. We have evidence on hand in a study that we are conducting at present that approximately the same percentage of normal persons without a history of pertussis possess pertussis-protective antibodies.

A group of 25 patients with clinically typical pertussis were tested, and 22, or 88 per cent, of them were found to have protective antibodies. This corresponds closely to the results that we obtained in our previous investigation.[1a] When the results are analyzed according to the period

of the disease, they show that protective antibodies were not found at the beginning but that they began to appear in some of the patients two to four weeks after the onset of the whoop and were present in all of the patients who were tested four to five and a half months after the onset of the infection. In most instances the patients possessed these antibodies in a high concentration after recovery. Thus the development of protective antibodies seems to parallel the development of immunity during convalescence or on recovery from the infection.

Agglutinins were found in only 3 of the 25 patients with pertussis that were tested. This is a much lower percentage of positive reactions than that obtained in our previous studies, in which we found that nearly 50 per cent of the patients had agglutinins. This difference, however, may be due to the difference in the period of the disease at which the examinations for agglutinins were made. In our previous studies most of the patients were examined early in the disease, whereas in this experiment 18 of the 25 patients were examined four to five and a half months after the onset of the infection.

Complement-fixing antibodies were found in 2 of the 7 patients with pertussis who were tested two to five weeks after the onset of the whoop but in none of those who were tested late in the disease. This is at variance with most of the results reported in the literature. After Bordet and Gengou's report [2] that the serums of persons convalescent from pertussis fixed complement when Haemophilus pertussis was used as an antigen, a number of workers reported similar results not only with the serums of convalescents but with the serums of patients in the preparoxysmal and paroxysmal stages. (A complete review of the literature has been given by Olmstead and Luttinger [3] and Weichsel and Douglas.[4]) Thus Friedlander and Wagner [5] found the antibodies in the serums of 11 of 12 patients in the preparoxysmal stage and of all of 18 patients in the paroxysmal stage. Olmstead and Luttinger [3] found that 15 (32.5 per cent) of 46 patients with pertussis had strongly positive reactions (3 plus or 4 plus), 23 weakly positive and 9 negative within four days to five months after the onset of the disease. Winholt [6] obtained positive results in two weeks but found the reaction stronger

2. Bordet, J., and Gengou, O.: Ann. Inst. Pasteur **20**:731, 1906; **21**:720, 1907; Centralbl. f. Bakt. (Abt. 1) **66**:276, 1912.

3. Olmstead, M., and Luttinger, P.: Complement Fixation in Pertussis, Arch. Int. Med. **16**:67 (July) 1915.

4. Weichsel, M., and Douglas, H. S.: J. Clin. Investigation **16**:15, 1937.

5. Friedlander, A., and Wagner, E. A.: Diagnosis of Whooping-Cough by the Complement-Deviation Test: Preliminary Note, J. A. M. A. **62**:1008 (March 28) 1914; Diagnosis of Whooping-Cough by the Complement-Fixation Test, Am. J. Dis. Child. **8**:134 (Aug.) 1914.

6. Winholt, W.: J. Infect. Dis. **16**:397, 1915.

after eight to ten weeks. Chievitz and Mayer [7] and Giese [8] obtained a high percentage of positive reaction from three weeks to five months after the onset of the disease. Madsen [9] obtained positive results regularly from the first week to the seventh week. He found that after that the percentage decreased slowly. Weichsel and Douglas [4] obtained positive results in 80 per cent of persons with whooping cough after the second week. They found that in most of them the reaction remained positive five to eight months. On the other hand, Fraenkel [10] obtained only 1 positive reaction among 5 convalescents; Wallstein [11] found all of 9 patients to have negative reactions after one to nine weeks of the disease; Baechner and Menschikoff [12] had negative results in the first to the sixth week of the paroxysmal stage, and Poleff [13] obtained negative results in the late stage of pertussis.

These discrepancies are no doubt due to the differences in the methods of testing, as well as the criterion of a positive reaction. Thus Chievitz and Mayer [7] considered the result positive when there was less than 70 per cent hemolysis. They stated that "complement fixation is most often feeble in pertussis," and some patients had to be tested several times before a positive reaction was obtained. Giese [8] found that 11.9 per cent of his control subjects gave a positive reaction and that 5 patients with scarlet fever and 4 with diphtheria also gave positive results. Weichsel and Douglas [4] found that 5 per cent of "normal children" and 13 per cent of "normal" adults had positive complement fixation.

We found that even with carefully standardized specific antigens nonspecific complement fixation may be obtained when more than 0.02 cc. of the patient's serum is used and that partial nonspecific fixation may be obtained with less than 0.02 cc. of heterologous immune serum when the tests are read after a short period of incubation. Therefore, in order to obtain strictly specific complement fixation the results were considered positive only when 0.02 cc. or less of the serum gave complete fixation when incubated for one hour at 37 C. after the sensitized cells were added. Incomplete or partial fixation was recorded as negative. Each test, however, was controlled by means of a standard positive serum, and a test was considered valid only when the titer of this control positive serum remained constant. This method of testing admittedly will not detect weakly positive reactions, but we felt that it was more important to

7. Chievitz, I., and Mayer, A. H.: Ann. Inst. Pasteur **30**:503, 1916.
8. Giese, H.: Ann. Inst. Pasteur **32**:522, 1918.
9. Madsen, T.: Boston M. & S. J. **192**:50, 1925.
10. Fraenkel, C.: München. med. Wchnschr. **55**:1683, 1908.
11. Wallstein, M.: J. Exper. Med. **11**:41, 1909.
12. Baechner and Menschikoff: Centralbl. f. Bakt. (Abt. 1) **61**:218, 1911.
13. Poleff, L.: Centralbl. f. Bakt. (Abt. 1) **69**:23, 1913.

obtain specific results than to raise the percentage of positive reactions by including weak or doubtful ones.

A group of 47 persons were tested who were intimately and repeatedly exposed to patients with active pertussis. Twenty-four, or 51 per cent, of them had protective antibodies, 8 (17 per cent) had agglutinins and 3 (6.3 per cent) had complement-fixing antibodies. Forty-two persons in this group had head colds or coughs, and 5 were well at the time of the test (four to five weeks after exposure). None of them had clinical symptoms of pertussis subsequently. The percentage of persons in this group who had protective antibodies after exposure was slightly higher in those in whom a mild infection developed than in those who remained well. These results show that exposure to active pertussis stimulates protective antibodies in a large percentage of persons who either remain well or have a mild atypical infection which under ordinary circumstances would not be diagnosed as pertussis. These observations emphasize the unreliability of a history that a patient has not had pertussis.

Fifty-five persons were tested who had no known exposure to patients with active pertussis but in whose cases exposure could not be excluded because they intermingled with the inmates of the other cottages. Forty-seven persons in this group had head colds or coughs at the time of the test. Ten of these, or 18.1 per cent, had protective antibodies and 8, or 14.5 per cent, had agglutinins. Six persons who had sore throats had no pertussis antibodies. Two persons were well, and neither of them had protective or complement-fixing antibodies; 1 had a low titer of agglutinins and the other had none. No complement-fixing antibodies were found in this group. Thus, in a group in which exposure to pertussis was possibly transitory the percentage of persons who had protective antibodies was only slightly higher than in the "normal" population at the institution.

Thirty patients were tested who had head colds and coughs but no known or probable exposure to pertussis at the institution, since they were permanently confined in segregated cottages. Three of these patients, or 10 per cent, had protective antibodies; 1 of these 3 also had agglutinins and another had complement-fixing antibodies. The results obtained in this group show that other infections of the respiratory tract, such as colds, do not stimulate pertussis-protective antibodies, since the percentage of positive reactions in this group did not exceed that of the "normal" population.

The reliability of the mouse protection test in detecting specific pertussis-protective antibodies was questioned by Mathieson and Clark,[14] who obtained protection against H. pertussis when they used diphtheria

14. Mathieson, D. R., and Clark, L. T.: J. Bact. **41**:68, 1941.

antitoxin, concentrated antipneumococcus serum, anti-Brucella-bronchiseptica serum and normal horse serum. The nonspecific protection that they obtained was undoubtedly due to their method of testing. They injected 0.5 cc. of the serum intraperitoneally one-half hour previous to the intraperitoneal inoculation of the culture. We found in our earlier investigations [1] that 0.2 cc. of normal serum gave protection when it was administered intraperitoneally but that the same amount of serum gave no protection when it was injected intramuscularly. Since then we have tested diphtheria antitoxin, antimeningococcus serum, antimeningococcus antitoxin, anti-influenza serum, concentrated antipneumococcus serum and normal horse serum by the intramuscular method and have obtained no protection with these serums.

TABLE 7.—*Summary of the Results Obtained in Study of Pertussis Antibodies in Persons Who Had Pertussis, in Persons Who Were in Contact with Patients with Active Cases of Pertussis and in Persons Who Had No Known Exposure to This Disease*

Total Tested—272 Serums, from 229 Persons

Groups	Number Tested	Positive Results					
		Aggl.		C.-F.		Mouse Protection	
		No.	%	No.	%	No.	%
1. Patients with pertussis	25.....	3	12	2	8	22	88
2. Persons intimately exposed to patients with active pertussis	42 with respiratory illness.....	7	16.6	3	7.1	22	52.3
	5 without illness..	1	*	0	0	2	*
Total	47	8	17	3	6.3	24	51
3. Persons possibly exposed	47 with respiratory illness.....	7	14.8	0	0	10	21.2
	6 with sore throat	0	0	0	0	0	0
	2 without illness..	1	*	0	0	0	0
Total	55	8	14.5	0	0	10	18.1
4. Persons with no known exposure	30 with respiratory illness.....	1	3.3	1	3.3	3	10
	72 without illness..	4	5.5	0	0	11	15.2
Total	102	5	4.9	1	0.98	14	13.7

* The percentage was not calculated when the group contained less than 25 persons.

CONCLUSIONS

Protective antibodies were found in all of the patients who had clinically typical pertussis when they were tested four to five and a half months after the onset of the disease. These antibodies were not found in the first week of the infection but were present in 4 of 7 patients (57 per cent) after two to four weeks. The development of protective antibodies seems to parallel the development of immunity during con-

valescence or after recovery from the disease, and when these antibodies are present they may be taken as presumptive evidence of immunity to pertussis.

Agglutinins were found in very few of the patients with pertussis studied in this series. Complement-fixing antibodies were found in 2 of the patients who were tested early in the infection but in none of those who were tested later. The results obtained in this investigation as well as in our previous studies show that the presence of these two antibodies cannot be taken as an index of immunity, since they were seldom present during convalescence or after recovery and when they were present their titers did not correspond either to the duration of the illness or to the protective power of the serum.[1a]

Evidence is presented that protective antibodies are stimulated by exposure to active pertussis in a large percentage of persons in whom there developed a mild atypical infection that would ordinarily not be diagnosed as pertussis and in some persons who showed no symptoms of illness after exposure.

Protective antibodies were found in 15.2 per cent of physically healthy children and adults who had no history of pertussis; in 10.3 per cent of patients who had head colds and coughs but no known exposure to pertussis, and in 18.5 per cent of persons who may have had transitory exposures to this disease. The presence of these antibodies in persons who had no known recent exposure to pertussis should be attributed to subclinical or mild unrecognized previous infections. That these antibodies are not stimulated by other infections of the respiratory tract is shown by the fact that the percentage of positive reactions among the patients with colds and coughs who had no known exposure to pertussis did not exceed that of the "normal" population.

Testing for protective antibodies should be helpful in selecting nonimmune persons for vaccination to evaluate the immunizing power of pertussis vaccines. Until now susceptible persons were selected for such studies on the basis of absence of a history of previous infection. From the evidence presented in this paper a history that a person has not had the disease cannot be relied on. The method of testing for protective antibodies also promises to be of value in determining the response to vaccination in human beings.[1b]

Testing for protective antibodies as a means of diagnosis would be of value only in excluding doubtful cases of pertussis when these antibodies are not present late in the infection.

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METHOD OF ASSAYING TRYPSIN SUITABLE FOR ROUTINE USE IN DIAGNOSIS OF CONGENITAL PANCREATIC DEFICIENCY

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The diagnosis of congenital pancreatic deficiency can be established by the determination of the concentration of pancreatic enzymes in the duodenal juice in suspected cases.[1] Of all the diagnostic methods explored, the assay of trypsin has been found to be the most valuable procedure. The method used for the determination of trypsin in the previous study was a viscosimetric one chosen for reliability and sensitivity. This method has the disadvantage of requiring a fairly elaborate equipment, much of which is not found in a hospital routine laboratory. Since the difference between the level of trypsin in congenital pancreatic deficiency and that in other varieties of the celiac syndrome is a wide one, a less sensitive and less elaborate method should be adequate for diagnosis and more practical for routine use. Several methods were tried, and the method of Fermi,[2] modified by Palitzsch and Walbum [3] and again by ourselves, was selected as one which combines simplicity with a degree of accuracy adequate for diagnostic purposes.

Parallel determinations by the viscosimetric method and by the modified Fermi method were made on 28 samples of duodenal juice. These were obtained from patients with a variety of diseases, including 4 with congenital pancreatic deficiency. The method of obtaining the duodenal juice and the procedure of the viscosimetric method have been

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1. Andersen, D. H.: Pancreatic Enzymes in the Duodenal Juice in the Celiac Syndrome, Am. J. Dis. Child. **63**:643 (April) 1942.

2. Fermi, C.: Reagenten und Versuchsmethoden zum Studium der proteolytischen und gelatinolytischen Enzyme, Arch. f. Hyg. **55**:140, 1906.

3. Palitzsch, S., and Walbum, L. E.: Ueber die optimale Wasserstoffionenkonzentration bei der tryptischen Gelatinverflüssigung, Biochem. Ztschr. **47**:1, 1912.

previously described.[1] The modified Fermi method is carried out as follows:

The substrate is a 7.5 per cent solution of Knox gelatin, obtained from the local grocer. In a 50 cc. beaker is placed 18.75 Gm. of gelatin. About 40 cc. of cold distilled water is gradually added, and the mixture is stirred until it is a semiliquid paste free from lumps. This paste is transferred through a small funnel to a 250 cc. volumetric flask, and the beaker and funnel are washed with about 100 cc. of water. The flask is heated on a water bath, with occasional shaking, until the solution is clear. It is then cooled, made up to volume with water and replaced on the water bath until the gelatin is entirely melted. The flask is shaken until the contents appear homogeneous. The gelatin is transferred to a

Comparison of Assay of Trypsin by Modified Fermi and Viscosimetric Methods in 28 Cases

	Fermi Method—First Liquefaction		Viscosimetric Units		
Tube	Cc. of Juice	No. of Cases	Mean	Maximum	Minimum
1	0.00125	0	...	...	...
2	0.0025	1	112	112	112
3	0.005	10	270	713	87
4	0.01	9	112	305	58
5	0.02	3	52	67	41
6	0.04	1	24	24	24
7	0.08	0	..	..	..
8	0.16	0	..	..	..
9	0.32	1*	5	5	5
No liquefaction	....	3*	1.3	4	0

* Patients with congenital pancreatic deficiency.

stock bottle, and a small amount of thymol is added. When stored in the refrigerator the substrate can be used for at least six weeks.

The substrate should be left to melt in an incubator at a temperature of 37 C. for approximately one hour before using. Twenty Wassermann tubes are set in a rack in pairs and labeled from 1 to 10; 2 cc. of melted substrate is placed in each with a transfer pipet. One cubic centimeter of duodenal juice is placed in a 10 cc. volumetric flask and made up to volume with a 5 per cent solution of sodium bicarbonate, this giving a 1 : 10 dilution. One cubic centimeter of this material is placed in a second 10 cc. flask and made up to volume in the same way, with a resulting 1 : 100 dilution. Each of the first pair of tubes then receives 0.125 cc. of the 1 : 100 dilution, measured with a 1 cc. Mohr graduated pipet, and 1.875 cc. of 5 per cent sodium bicarbonate solution; this makes a total volume of 4 cc. in each tube, of which 0.00125 cc. is duodenal juice. The remaining tubes are set up in a similar manner; the second pair each receives 0.25 cc. of 1 : 100 dilution, and the following ones 0.5 and

1.0 cc. of the 1 : 100 dilution, then 0.2, 0.4, 0.8 and 1.6 cc. of the 1 : 10 dilution and finally 0.32 cc. of the undiluted juice in a total volume of 4 cc. The remaining pair of tubes contains no juice and serves as a control. Each of the tubes is then covered by the thumb and inverted several times to insure mixing, with care to handle the control tubes first, then the pair with the lowest concentration of juice, and so on in order. The rack of tubes is incubated for one hour at 37 C. and then left in a refrigerator at about 4 C. Twenty to twenty-four hours later the tubes are removed from the refrigerator and read immediately. The lowest dilution in which the gelatin has liquefied in one or both tubes is considered as the reading.

A comparison of the results obtained by this method with the viscosimetric units of the same samples is given in the accompanying table. It will be seen that there is a safe margin between the figures obtained in 4 samples from patients with pancreatic deficiency and those obtained from any of the other patients. Of the group without pancreatic deficiency, the 2 lowest figures (24 and 41 viscosimetric units) were obtained from marasmic infants.

SUMMARY AND CONCLUSIONS

A simple method of determining trypsin activity, adapted to the facilities of a hospital routine laboratory, has been described. Comparison of this method with the more elaborate and more accurate viscosimetric method has been made with 28 samples of duodenal juice from patients with a variety of conditions, including 4 infants with congenital pancreatic deficiency. The simpler method has been found adequate for the diagnosis of this disease.

IS THE PRESENCE OF BILE AND FOOD IN THE SMALL INTESTINE NECESSARY FOR THE FORMATION OF PROTHROMBIN?

STUDIES ON THREE INFANTS, ONE WITH CONGENITAL ABSENCE OF THE GALLBLADDER AND EXTRAHEPATIC DUCTS AND TWO WITH CONGENITAL ATRESIA OF THE ESOPHAGUS

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Disturbances of the coagulation of the blood may occur if the plasma prothrombin content is below 20 per cent. Such a reduction is presumed to occur under conditions which affect the supply, the absorption or the utilization of vitamin K. In the adult it is difficult to demonstrate an actual deficiency of vitamin K in the diet. The explanation given is that the bacterial flora of the intestine furnishes an intrinsic source of vitamin K which is sufficient to give an adequate supply even if the diet itself is deficient or lacking in the vitamin. In the newborn infant, however, there is a decrease in the plasma prothrombin level during the first three days of life, followed by a rise to normal values. Quick [1] has suggested that this is due to a prompt establishment of bacterial flora in the intestine following the ingestion of food. Salomonsen and Nygaard [2] and Gellis and Lyon [3] have both reported on series of newborn infants in which the plasma prothrombin level was considerably higher in those infants given an artificial feeding immediately after birth than in control infants that were sent to the breast thirty-six or forty-eight hours after birth.

From the Department of Pediatrics, Rush Medical College and the Presbyterian Hospital, Chicago. Funds for this study were obtained by a grant from the Elizabeth McCormick Fund of the Institute of Medicine, Chicago.

Read at a meeting of the Chicago Pediatric Society, Dec. 16, 1941. The discussion appears with the transactions of that society, this issue, page 986.

1. Quick, A. J., and Grossman, A. M.: The Nature of Hemorrhagic Disease of the Newborn, Am. J. M. Sc. **199**:1 (Jan.) 1940.

2. Salomonsen, L., and Nygaard, K. K.: Prothrombin Content in Relation to Early and Late Feeding in the Newborn, Acta pædiat. **27**:209, 1939.

3. Gellis, S. S., and Lyon, R. A.: The Influence of the Diet of the Newborn Infant on the Prothrombin Index, J. Pediat. **19**:495 (Oct.) 1941.

Interference with absorption is presumed to occur with obstructive jaundice and with biliary fistulas. The explanation given is that the presence of bile in the intestinal tract is necessary for the absorption of the vitamin. It is assumed, moreover, that interference with utilization may occur in other diseases that may affect intestinal functions, such as ulcerative colitis and sprue.

This presupposes that for the formation of prothrombin two factors are necessary: food to furnish the vitamin or to synthesize it by bacteria in the intestine, and the presence of bile salts in the intestine. For this reason the cases of 3 infants in each of whom one of these factors was absent are presented.

REPORT OF CASES

CASE 1.—*Absence of food.* A girl born three weeks prematurely, weighing 5 pounds 7 ounces (2,466 Gm.), had a history of vomiting all feedings with considerable mucus. Roentgen examination after administration of barium sulfate by mouth showed atresia of the esophagus. The parents refused to permit operation but insisted that the child be given blood transfusions and subcutaneous injections of salt solution. An estimation of the plasma prothrombin was made on the fifth day, just before the first transfusion. None was made thereafter. The child died on the fourteenth day of life. Autopsy showed not only complete atresia of the esophagus but atresia of the duodenum.

CASE 2.—*Absence of food.* A girl was born at full term, weighing 7 pounds (3,175 Gm.). Examination at birth, after the nurses' report of considerable vomiting of mucus, showed atresia of the esophagus with a fistula into the bronchi on both sides at the bifurcation of the trachea. The parents refused to permit operation; so no food or fluid was ever given this child, enterally or parenterally. Meconium was passed normally for three days, after which there were no further bowel movements. Death occurred on the fourteenth day.

CASE 3.—*Absence of bile.* A full term girl, weighing 7 pounds 5 ounces (3,317 Gm.) at birth, passed meconium stools for five days; passage of acholic stools then began and persisted until she was 5 months of age. For the next month there was a thin yellow coating on the outside of the stool, which was acholic inside. An exploratory operation was performed on the child's twenty-sixth day of life, and she was found to have complete obliteration of the gallbladder and extrahepatic ducts. The abdomen was closed, and nothing further was done. The child lived for six months on a feeding rather low in fat and high in carbohydrate. Physically the child conformed to the fate of such children. She was deeply jaundiced, with an enlarged liver (liver function plus 4 [Hanger]). The icterus index was 165, and the cholesterol content of the blood was 250 mg. per hundred cubic centimeters.

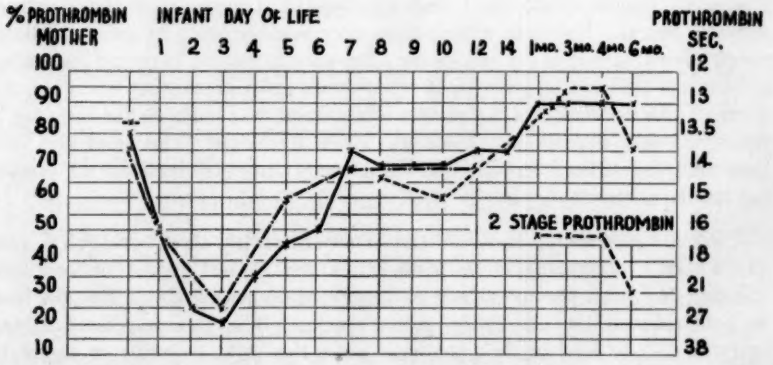
COMMENT

The results of plasma prothrombin studies are shown in the chart. The method of Quick was used in cases 1 and 2, and both that of Quick and that of Warner, Brinkhaus and Smith, in case 3. These were the described macromethods for venous blood. Thromboplastic material was

freshly checked with normal blood before each estimation. The plasma prothrombin curve for normal newborn infants is the one previously reported by us.[4]

It will be observed that the plasma prothrombin curve for the infant with atresia of the esophagus (case 2) is similar to that of normal newborn infants. Estimations were made on the first, third, fifth, seventh and twelfth days of life. Only one estimation was made in case 1, the value being 45 per cent on the fifth day of life, exactly the same as that of the normal newborn infants. This has not been charted. No further plasma prothrombin estimations were made on this infant, as they would have been influenced by the transfusions.

In case 3, that of the infant with atresia of the bile ducts, no estimations of plasma prothrombin were made until the eighth day of life. The


% PROTHROMBIN MOTHER
INFANT DAY OF LIFE
1 2 3 4 5 6 7 8 9 10 12 14 1mo. 3mo. 4mo. 6mo.
PROTHROMBIN SEC.
100 90 80 70 60 50 40 30 20 10
12 13 13.5 14 15 16 18 21 27 38
2 STAGE PROTHROMBIN

Prothrombin studies on an infant with congenital atresia of bile ducts (dash line) and on an infant with congenital atresia of the esophagus (case 2) (dot and dash line). The solid line indicates the average for normal newborn infants.

jaundice was no deeper than in most infants, and the meconium masked the acholic stool until this time, when the condition was first suspected. It will be observed that the plasma prothrombin values are not particularly different from those of normal infants, being slightly lower for the second week of life and slightly higher for the first four months of life. The last estimation, made when the patient was 6 months old, showed the value to be slightly lower than normal. By the two stage method, however, the plasma prothrombin was considerably below normal values, varying from 32 to 48 per cent. On the tenth day of life it was 60 per cent, and when next estimated, just before operation, on the twenty-fifth day of life, it had increased to 85 per cent. After the operative examination it steadily climbed to 95 per cent and remained at this

4. Sanford, H. N., and Shmigelsky, I.: Is the Administration of Vitamin K to the Newborn of Clinical Value? J. A. M. A. **118**:697 (Feb. 28) 1942.

value for the next four months. At the last estimation, after six months of life, it had dropped to 75 per cent.

It must be emphasized that this infant never received any vitamin K, blood transfusions or bile salts. She had been fed since birth on a formula of lactic acid milk and cane sugar, with orange juice and concentrated cod liver oil. Her icterus index was 125 on the tenth day of life and 165 at the age of 6 months. Her blood cholesterol content had risen from 165 mg. per hundred cubic centimeters at 1 month to 250 mg. at 6 months.

Congenital abnormalities of the gallbladder and extrahepatic ducts are not entirely incompatible with life. Stolkind [5] in 1939 was able to find 124 recorded instances of congenital absence of the gallbladder in which the children had lived from one to twelve months after birth, and 8 in which they had lived from one to three and one-half years. Since this report Finlayson [6] has described a case in which an exploratory operation was done when the patient was at 3 months of age and absence of bile ducts and of the gallbladder was found. The child lived three and a half years. Donovan [7] has reported on 2 children who at operation were thought to have complete obliteration of the gallbladder and extrahepatic ducts and who were alive two and one-half years after the operation.

Children with such a condition are far from normal. Their growth is stunted. The stools are acholic, and the digestion is poor. They are deeply jaundiced, usually having an icterus index above 100. Sooner or later cholesterol is deposited in the skin, and the blood cholesterol level is correspondingly high. At autopsy considerable cirrhosis and enlargement of the liver are found. These various manifestations are due to the absence of bile in the intestines, whereby the fat digestion is hampered, and to the absorption of bile that is unable to reach the intestine by the blood stream.

In none of the reports of congenital absence or atresia of the bile ducts has there been any mention of abnormal bleeding. Many of the children underwent an exploratory operation, as did 1 of our patients, but in no case is there any mention of postoperative bleeding. Watkins and Wright [8] studied the coagulation time of a baby with congenital atresia of the bile ducts that lived for fifteen months and found it to be

5. Stolkind, E.: Congenital Abnormalities of the Gall Bladder and Extra Hepatic Ducts, Brit. J. Child. Dis. **36**:295 (Dec.) 1939.

6. Finlayson, C.: Congenital Obliteration of the Bile Ducts, Arch. Dis. Childhood **12**:153 (Oct.) 1937.

7. Donovan, E. J.: Congenital Atresia of the Bile Ducts, Ann. Surg. **106**:737 (Oct.-Dec.) 1939.

8. Watkins, A. G., and Wright, G. P.: Congenital Atresia of Bile Ducts, Lancet **1**:1066 (May 20) 1933.

normal throughout. Quick [9] estimated the prothrombin level in an infant that at operation at the age of 2 months was found to have absence of hepatic ducts and no bile in the cystic ducts, common duct or gallbladder. He stated "in this type of case one could expect the development of vitamin K deficiency, but the prothrombin remained normal and no signs of bleeding tendency were observed."

It was unfortunate that no estimations of plasma prothrombin were made during the first week of life for the infant under our care. Certainly, however, there was no tendency to abnormal external bleeding, or it would have been observed. When the first estimation was made, on the eighth day of life, the plasma prothrombin was found to be similar to that of a normal newborn infant. As we have found that the diminution of plasma prothrombin influences the rapidity of its return to normal values, we feel safe in assuming that the plasma prothrombin did not fall below a normal value for a newborn infant during the first week of life. During the next four months of the child's life the plasma prothrombin level was even slightly above that found in the normal infant. It was only in the last month, when evidences of decreased hepatic function were more pronounced, that the plasma prothrombin fell somewhat under normal values.

It is of interest to note the difference in value of the plasma prothrombin as determined by the two methods, the one of Quick and the one of Warner, Brinkhaus and Smith. We have observed that the biphase method of Warner, Brinkhaus and Smith will yield values 15 to 20 per cent less than those obtained by the method of Quick. The case of this infant with absence of the gallbladder and bile ducts is the first instance in which we have observed so marked a difference between the results of these two methods, being uniformly 40 per cent. When the child was 6 months old, one week before death, the plasma prothrombin value by the Quick method was 75 per cent and by the biphase method 32 per cent. It must be remembered, however, that neither of these methods, or in fact any method, measures the prothrombin directly as such. All they show is the time necessary to convert the existing plasma prothrombin to thrombin in the presence of excess thromboplastin and a measured amount of calcium; then the time necessary to convert the soluble fibrinogen to the insoluble fibrin by this formed thrombin. As the biphase method eliminates the last step in the reaction (the fibrinogen being measured), this would indicate some difference in the combining power of this infant's plasma prothrombin rather than a diminution—inasmuch as the Quick method shows that its plasma prothrombin exists in normal amounts. Neither of these estimations makes any great differ-

9. Quick, A. J.: The Nature of the Bleeding in Jaundice, J. A. M. A. **110**:1658 (May 14) 1938.

ence as long as the blood coagulates normally. In this infant normal coagulation of the blood was continuous.

Owing, therefore, to certain congenital malformations that are present only in the period immediately after birth and in early infancy, we are able to show that bile in the small intestine is not necessary for the formation of plasma prothrombin, nor is the presence of food in the intestine. In an infant with congenital absence of the gallbladder and bile ducts as shown by the icterus index, acholic stools and exploratory operation, no bile entered the small intestine for at least five months. Yet the plasma prothrombin remained at a normal level. In 2 infants with congenital atresia of the esophagus in whom no food could possibly enter the stomach or small intestine, the plasma prothrombin remained at a normal level throughout life.

It would seem, therefore, that the present explanation of the synthesis of vitamin K by bacteria from food in the small intestine and the necessity of bile for the conversion of vitamin K is untenable. While there may be other factors, at the present time unknown, which cause this conversion, it appears to us that the liver is the principal source of this vitamin and that it will continue to form it independently of extrinsic causes until its functions are diminished by serious damage.

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RESPIRATORY METABOLISM IN INFANCY AND IN CHILDHOOD

XXV. THE SPECIFIC DYNAMIC ACTION OF AMINO ACIDS IN INFANTS

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The storage, utilization and breakdown of proteins in the immature, rapidly growing organism differ from those in the adult in many important respects. One potentially useful means of investigating the differences and of obtaining information about protein metabolism in general resides in the special property possessed by proteins and by some of the amino acids of raising the metabolic rate of animal organisms to a far greater extent than equal amounts of fat or carbohydrate. Although this phenomenon, traditionally termed "specific dynamic action," has not yet been completely explained, it has served as a valuable tool in many studies. The detailed history of the earlier animal experiments is recounted in Graham Lusk's book,[1] while more recent work by many investigators has been reviewed by Borsook.[2]

A well controlled study of the specific dynamic action of foodstuffs in normal infants was made by Levine, Wilson, Berliner and Rivkin,[3] who reviewed the earlier work which they confirmed and extended. In their observations, the greatest calorigenic effect was obtained with mix-

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A preliminary report of the data presented in this paper was made at the annual meeting of the Society for Pediatric Research, Atlantic City, N. J., May 7, 1941.

1. Lusk, G.: The Elements of the Science of Nutrition, ed. 4, Philadelphia, W. B. Saunders Company, 1928.

2. Borsook, H.: The Specific Dynamic Action of Protein and Amino Acids in Animals, Biol. Rev. **11**:147 (April) 1936.

3. Levine, S. Z.; Wilson, J. R.; Berliner, F., and Rivkin, H.: The Respiratory Metabolism in Infancy and in Childhood: VI. The Specific Dynamic Action of Food in Normal Infants, Am. J. Dis. Child. **33**:722 (May) 1927.

tures of food in which protein predominated. Levine, Wilson and Gottschall [4] demonstrated that marasmic infants did not differ significantly from healthy full term babies in their specific dynamic response to foods. Perhaps because these results were comparable to those of reported animal experiments, little further work in this field was done until 1937-1938, when Gordon [5] attempted to reproduce these observations in premature infants. Contrary to expectation, no increase in heat production occurred when the protein intake of the infants was increased.

Soon thereafter, a different approach to the question of amino acid metabolism in premature infants resulted in the discovery by Levine, Marples and Gordon [6] that when such infants have a protein intake of 5 Gm. or more per kilogram per day derivatives of aromatic amino acids appear in the urine in fairly large amounts, particularly l-parahydroxyphenyllactic and parahydroxyphenylpyruvic acids. This excretion is accentuated by the feeding of tyrosine or phenylalanine and diminished or abolished by the administration of l-ascorbic acid.

A possible relationship between this defect in utilization of aromatic amino acids and the absence of specific dynamic action of high protein feeding in premature infants prompted the present investigation. In addition to the aromatic compounds tyrosine and phenylalanine, a simple aliphatic amino acid, aminoacetic acid, was chosen for study.

The only reported data on the specific dynamic action of these individual amino acids are those in the series on animal calorimetry made in Lusk's laboratory, especially by Rapport and Beard [7] and Weiss and Rapport.[8] When these observers gave to a 6.5 Kg. dog 10 Gm. of aminoacetic acid, phenylalanine or tyrosine, the metabolic rate was raised

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4. Levine, S. Z.; Wilson, J. R., and Gottschall, G.: The Respiratory Metabolism in Infancy and in Childhood: X. The Respiratory Exchange in Marasmus; Specific Dynamic Action of Food in Normal and in Marasmic Infants, Am. J. Dis. Child. **36**:740 (Oct.) 1928.

5. Gordon, H. H.: Unpublished data, 1939.

6. (*a*) Levine, S. Z.; Marples, E., and Gordon, H. H.: A Defect in the Metabolism of Aromatic Amino Acids in Premature Infants: The Role of Vitamin C, Science **90**:620 (Dec. 29) 1939. (*b*) Levine, S. Z.; Marples, E., and Gordon, H. H.: A Defect in the Metabolism of Tyrosine and Phenylalanine in Premature Infants: I. Identification and Assay of Intermediary Products, J. Clin. Investigation **20**:199 (March) 1941. (*c*) Levine, S. Z.; Gordon, H. H., and Marples, E.: A Defect in the Metabolism of Tyrosine and Phenylalanine in Premature Infants: II. Spontaneous Occurrence and Eradication by Vitamin C, ibid. **20**:209 (March) 1941.

7. Rapport, D., and Beard, H. H.: The Effect of Protein Split-Products upon Metabolism: II. The Individual Amino Acids of Fraction 1 of the Butyl Alcohol Extraction and Their Relation to the Specific Dynamic Action of Protein, J. Biol. Chem. **73**:299 (May) 1927.

8. Weiss, R., and Rapport, D.: The Interrelations Between Certain Amino Acids and Proteins with Reference to Their Specific Dynamic Action, J. Biol. Chem. **60**:513 (July) 1924.

by 17 per cent or more for several hours. By analogy, similar doses of these amino acids (1 to 2 Gm. per kilogram of body weight) given to infants might be expected to produce increases in metabolic rate readily measurable by available methods. Accordingly, a series of observations was made in a group of 10 premature infants, to which 3 full term infants were added after Levine, Gordon, and Marples [6c] had discovered that the metabolic defect which had previously been described in premature infants might also be exhibited by full term babies after the ingestion of tyrosine.

APPARATUS AND EXPERIMENTAL PROCEDURE

Determinations of Respiratory Metabolism.—All observations were made in the air-conditioned suite of the metabolism unit of the children's clinic at the New York Hospital.[9] The original apparatus for infant calorimetry has undergone considerable modification.[10] A respiration chamber of 120 liter capacity for full term infants [8] and a chamber of only 21 liter volume for premature infants [9] have been added, and in 1940 the open circuit system for the determination of oxygen consumption and carbon dioxide production was substituted for the closed circuit system.[11] The apparatus used in the studies to be reported was that last described except that in a few observations on full term infants the larger (120 liter) chamber was used. The rate of ventilation was adjusted to supply 100 liters of air per hour per kilogram of body weight of the subject. The temperature within the chamber was usually between 26 and 29 C.; in a few instances, a higher temperature was maintained, with little clothing on the infant. The observations at the higher temperatures totaled 6 (observations 7-1, 7-3, 7-4, 7-5, 7-16 and 7-17, table 2).

The alcohol checks which were made during the period of observations are recorded in table 1.

Subjects and Plan of Observation.—Ten male premature infants and 3 male full term infants were studied. Essential information about these babies is listed in table 2. Three subjects were observed after administration of two or more different amino acids; in 3 instances the same amino acid was given more than once to the same baby; in each of the remaining 7 infants the effect of only one dose of one amino acid was studied. A total of 20 amino acid observations were made, each with at least 1 control observation.[12]

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9. Gordon, H. H., and Levine, S. Z.: Respiratory Metabolism in Infancy and in Childhood: XVIII. The Respiratory Exchange in Premature Infants—Basal Metabolism, Am. J. Dis. Child. **52**:810 (Oct.) 1936.

10. Levine, S. Z., and Wilson, J. R.: The Respiratory Metabolism in Infancy and in Childhood: I. Basal Metabolism of Children, Am. J. Dis. Child. **31**:323 (March) 1926. Wilson, J. R.; Levine, S. Z., and Rivkin, H.: The Respiratory Metabolism in Infancy and in Childhood: II. Ketosis and the Respiratory Exchange in Children, ibid. **31**:335 (March) 1926.

11. Gordon, H. H.; Levine, S. Z.; Deamer, W. C., and McNamara, H.: Respiratory Metabolism in Infancy and in Childhood: XXIII. Daily Energy Requirements of Premature Infants, Am. J. Dis. Child. **59**:1185 (June) 1940.

12. The term "control" rather than "basal" is purposely used, because the expression "basal metabolic rate" is usually restricted to the rate determined under resting, postabsorptive conditions. In practice, it is impossible to obtain a resting metabolic rate in a hungry infant. The rate is therefore determined after a small meal, while the infant is sleeping.

TABLE 1.—*Alcohol Checks for Experimental Period (1938-1941) in Terms of Averages per Hour*

Date	Minutes	No. of Periods	Alcohol, Gm.	Water			Carbon Dioxide			Oxygen			Respiratory Quotient (Theoretic, 0.667)		Calories, Theoretic
				Theoretic, Gm.	Found, Gm.	Percentage of Error	Theoretic, Liters	Found, Liters	Percentage of Error	Theoretic, Liters	Found, Liters	Percentage of Error	Found	Error	
12/ 2/38	60	2	0.93	1.229	1.277	+ 3.9	0.909	0.869	—4.4	1.364	1.313	—3.7	0.662	—0.005	6.62
12/13/38	135	3	0.95	1.252	1.276	+ 1.9	0.926	0.886	—4.3	1.389	1.331	—4.2	0.665	—0.002	6.74
1/27/39	135	3	0.89	1.170	1.204	+ 2.9	0.865	0.828	—4.3	1.298	1.256	—3.3	0.660	—0.007	6.30
4/ 5/39 *	30	1	3.13	4.122	4.234	+ 2.7	3.050	2.914	—4.5	4.576	4.390	—4.1	0.664	—0.003	22.19
5/17/39	95	2	0.72	0.947	1.004	+ 6.0	0.701	0.670	—4.4	1.051	1.010	—3.9	0.663	—0.004	5.10
6/28/39	90	2	0.76	0.994	1.033	+ 3.8	0.730	0.713	—3.0	1.103	1.066	—3.3	0.669	+0.002	5.35
7/12/39	180	3	4.41	5.792	5.519	— 4.9	4.286	4.077	—4.9	6.430	6.203	—3.5	0.657	—0.010	31.16
7/19/39 †	145	3	2.06	2.714	2.702	— 0.4	2.012	1.898	—5.5	3.018	2.861	—5.2	0.663	—0.004	14.64
6/ 3/40	60	1	1.61	2.120	2.059	— 2.9	1.552	1.511	—2.6	2.341	2.290	—2.2	0.660	—0.007	11.37
9/ 9/40	90	2	1.76	2.322	2.417	+ 4.1	1.700	1.653	—2.8	2.564	2.515	—1.8	0.657	—0.010	12.46
9/20/40	90	2	1.86	2.470	2.403	— 2.7	1.801	1.718	—4.6	2.718	2.578	—5.2	0.666	—0.001	13.17
10/ 9/40	90	2	1.61	2.134	2.199	+ 3.0	1.559	1.498	—3.9	2.353	2.265	—3.7	0.662	—0.005	11.40
11/20/40 †	90	2	2.64	3.500	4.302	+22.9	2.554	2.444	—3.1	3.852	3.664	—3.7	0.667	0	18.67
12/20/40	70	2	1.52	2.015	1.992	— 1.1	1.470	1.436	—2.3	2.218	2.160	—2.6	0.665	—0.002	10.76
1/24/41	100	2	1.91	2.540	2.582	+ 1.7	1.853	1.818	—1.9	2.796	2.755	—1.5	0.660	—0.007	13.55
Average			1.78	2.355	2.414	+ 2.5	1.731	1.662	—4.0	2.605	2.510	—3.6	0.662	—0.005	12.63

* Infant chamber.

† Infant chamber, dead space partially filled.

TABLE 2.—*Data on Subjects*

Subject	Birth Weight, Gm.	Day of Observation			Observation		Feeding					Ascorbic Acid Ingestion		Excretion of Derivatives of Aromatic Amino Acids
							Per Day		Last Feeding					
		Date	Age, Days	Weight, Gm.	Number	Kind *	Cal.	Protein, Gm.	Protein, Gm.	Amino Acid, Gm.	Nitrogen, Gm.	Days Preceding Observation	Daily Dose, Mg.	
G. C.	1,130	12/27/38	61	2,226	5-21	C	292	14.1	1.8		0.282	57	10 to 20	.....
		12/30/38	64	2,302	5-22	PA	318	15.3	1.9	1.0	0.383	60		
		1/11/39	76	2,560	5-23	C	341	12.6	1.6		0.251	72		
		1/13/39	78	2,640	5-24	G	341	12.6	1.6	5.0	1.185	74		
F. Z.	1,170	1/18/39	21	1,880	5-25	C	229 †	5.6	0.7		0.110	16		
		1/20/39	23	1,920	5-26	G	229 †	5.6	0.7	5.0	1.044	18	10	None
		1/24/39	27	2,060	5-27	G	269	12.9	1.6	5.0	1.044	22		
		1/26/39	29	2,160	5-29	C	269	12.9	1.6		0.251	24		
D. M.	2,150	2/16/39	16	2,260	5-31	C	269	12.9	1.5		0.235	8	10	None
		2/17/39	17	2,320	5-32	G	269	12.9	1.5	2.0	0.491	9		
R. G.	1,422	3/ 8/39	49	2,170	5-33	C	283	13.6	1.7		0.267	....	None ‡	
		3/10/39	51	2,220	5-34	PA	283	13.6	1.7	1.0	0.352	....		None
R. S.	1,900	5/ 3/39	34	2,680	5-41	PA	367	17.6	2.9	2.2	0.642	60	10 to 20	Marked
		5/ 4/39	35	2,760	5-42	C	367	17.6	2.9		0.455	61		
F. L.	1,650	6/14/40	55	2,800	6-1	C	335	11.8	1.5		0.235	....	None	
		6/17/40	58	2,890	6-2	PA	335	11.8	0.75 §	5.8	0.610	....	None	Marked (6-2)
		6/21/40	62	3,000	6-3	PA	335	11.8	0.75	5.8	0.610	2	500, 200	None (6-3)
R. E.	2,090	12/16/40	31	2,730	7-13	C	343	17.8	2.9		0.455	....	None	Marked
		12/18/40	33	2,810	7-14	PA	343	17.8	2.9	5.6	0.930	....		
A. L.	1,890	1/ 3/41	31	2,472	7-16	G	308	10.5	1.8	2.5	0.749	14	25	.....
		1/ 6/41	34	2,720	7-17	C	308	10.5	1.8		0.282	17		
D. P.	2,160	9/23/40	11	2,190	7-1	T	287 †	6.8	0.9	4.4	0.481	6	25	None
		9/30/40	18	2,366	7-3	C	332 †	7.8	1.0		0.157	13		
		10/ 2/40	20	2,458	7-4	T	332 †	7.8	1.0	4.9	0.536	15		
		10/ 4/40	22	2,560	7-5	G	?332 ‖	7.8 ‖	1.0	2.2	0.568	17		
L. S.	2,235	2/14/41	11	2,320	7-23	C	304 †	7.2	0.9		0.141	2	200	
		2/17/41	14	2,392	7-24	G	266 †	6.3	0.9	4.0	0.887	....	None ¶	.....
A. T. ‡	2,610	3/24/39	81	3,800	5-35	T	504	18.9	2.4	1.8	0.515	21	10 to 20	
		3/27/39	84	3,880	5-36	C	504	18.9	2.4		0.376	24		None
		3/31/39	88	4,020	5-37	PA	562	20.7	2.5	2.0	0.562	28		
		4/ 3/39	91	4,100	5-38	C	562	20.7	2.6		0.408	31		
		4/ 6/39	94	4,220	5-39	G	562	20.7	2.6	2.0	0.781	34		
R. J. ‡	2,570	5/29/39	37	3,040	5-44	T	391	18.8	2.4	3.0	0.608	7	20	Slight
		5/31/39	39	3,120	5-45	C	391	18.8	2.4		0.376	9		
H. G. ‡	3,180	11/25/40	42	3,540	7-8	C	373	18.8	3.1		0.487	7	25	.....
		11/27/40	44	3,620	7-9	PA	373	18.8	3.1	7.3	1.106	9		

* C, control; G, aminoacetic acid; PA, phenylalanine; T, tyrosine.
† Human milk; cow's milk mixtures (olac, alacta, etc.) in remaining observations.
‡ Had received ascorbic acid 10 mg. daily for 6 days and 20 mg. daily for 22 days, last dose 12 days before first calorimeter observation.
§ Half refused.
‖ Baby nursed by mother but given bottle (H. M.) for calorimetric observation.
¶ Received 25 mg. 2 days before test; none on day preceding.
‡ Full term infant.

The chronologic sequence was purposely varied; i. e. in some instances the control preceded, and in others it followed, the amino acid observation. The interval between individual observations was usually only one to three days. Despite this brief time interval, the possibility of increase in the control metabolic rate from day to day because of the rapidly changing body weight made it preferable to calculate the heat production on separate days in terms of calories per kilogram [13] per unit of time rather than on the basis of time alone.

The procedure in control observations was as follows: The infant was given a small feeding (usually one eighth of his total daily formula). The time of the last voiding was noted and the urine discarded. He was placed in the respiration chamber on a specially constructed mattress which permitted the separate collection of urine and feces under oil. The cover of the box was then closed and the ventilation system turned on. After a preliminary period, usually of forty-five minutes, the respiratory metabolism was determined for several periods of about thirty minutes each, during which the infant was closely watched through the glass windows in the cover of the chamber; any period in which there was crying or restlessness amounting to more than slight occasional movements in sleep was excluded from the calculations. The duration of observations generally ranged from the end of the first hour after feeding to two and a half or three hours after feeding. After removal of the baby from the calorimeter the time of voiding was again recorded and all of the urine passed during the interval was saved for quantitative nitrogen determination and in some instances for determination of derivatives of aromatic amino acids.

The amino acid observations were carried out in the same way as the controls with the following additions: The total dose of amino acid was administered by mouth along with an amount of formula equal to that ingested in the control period. Because of the bulk and limited solubility of some of the amino acids, the actual time required for feeding was sometimes prolonged. The first part of each observation was continued to about the third hour after feeding. At that time, in the majority of the observations the infant was removed from the chamber, given another small feeding equal to that in the control observation and replaced in the chamber and the observation was continued up to the sixth hour after ingestion of the dose of the amino acid. This procedure was followed in order to ascertain whether the specific dynamic action if detected in the first few hours was sustained, or if not detected was perhaps delayed.

Calculations.—The heat production in the control observations was calculated by the method of Lusk [1] according to his modification of the table of Zuntz and Schumburg.[14] In the observations following the ingestion of amino acids, the same method was used and in addition a calculation was made with the use of special factors derived for aminoacetic acid by Lusk,[15] for tyrosine by Lusk [16] and for

13. Although in the opinion of some authorities surface area standards are theoretically sounder, they are impractical for use with infants, since calculations of surface area dependent on height introduce another source of error.

14. Zuntz, N., and Schumburg, W.: Studien zu einer Physiologie des Marsches, Berlin, A. Hirschwald, 1901.

15. Lusk, G.: Animal Calorimetry: XI. An Investigation into the Causes of the Specific Dynamic Action of the Foodstuffs, J. Biol. Chem. **20**:555 (April) 1915.

16. Lusk, G.: Animal Calorimetry: V. Influence of the Ingestion of Amino Acids upon Metabolism, J. Biol. Chem. **13**:155 (Dec.) 1912.

phenylalanine by Rapport and Beard.[17] In applying these factors, the assumption was made that all of the urinary nitrogen excreted in excess of that excreted during the control period was derived from amino acid.[18]

RESULTS

Extent of Variation in Individual Control Observations and Periods.—In order to form an estimate as to what constitutes a significant increase in heat production above the control level, repeated observations were made on 2 infants. Infant G. C., in observations 5-21 (table 4) and 5-23 (table 3) produced 63.43 and 61.82 calories per kilogram per hour respectively, averaging 62.63. The deviation from the average was 0.81 calory, or 1.2 per cent. Infant F. Z., in observations 5-25 and 5-29 (table 3) produced 64.86 and 62.97 calories per kilogram per hour respectively, averaging 63.92 and varying from the average by 0.95 calory, or 1.5 per cent. Furthermore, the magnitude of variability in individual periods of the same control experiment was in most instances of the order of 1 to 4 per cent. The only subjects in whom variations were greater than 5 per cent were infant D. M., who showed in observation 5-31 (table 3) a difference among individual periods of 8.6 per cent, and infant R. E., who varied by 5.3 per cent in observation 7-13 (table 4). Except for these 2 subjects, an increase above the control level of 5 per cent or more could be considered as a significant specific dynamic effect.

Aminoacetic Acid.—After the ingestion of aminoacetic acid (table 3) in doses ranging from 0.47 to 2.6 Gm. per kilogram of body weight, it was observed that in every instance in which the dose was more than 1 Gm. per kilogram a definite increase in heat production took place. This also occurred in an observation (5-32) in which a smaller dose was given.[19] The rise in heat production followed one of two patterns:

17. Rapport, D., and Beard, H. H.: The Effect of Protein Split-Products upon Metabolism: I. The Fraction Extracted by and Precipitated in Butyl Alcohol (Fraction 1), J. Biol. Chem. **73**:285 (May) 1927.

18. Fortunately, the validity of this assumption is of academic interest only, since the actual values for total heat production obtained by the two methods of calculation differed by insignificant amounts. The usual difference was of the magnitude of 0.1 to 0.7 per cent, and the greatest difference was 0.85 per cent. The values given in tables 3, 4 and 5 are those calculated by the use of the special amino acid factors.

19. Two of these observations were complicated, one by the occurrence of a loose stool (observation 5-27) and another by vomiting (observation 5-32), before the beginning of the first period of observation. In the latter observation, a part of the test dose was lost. Four grams, or 1.72 Gm. per kilogram, was ingested, but only half of this amount was estimated to have been retained. In each instance, the observation was not begun until all symptoms had subsided and the infant was quiet and appeared comfortable. No regurgitation or evidence of distress was observed in any of the other observations.

TABLE 3.—*Specific Dynamic Action of Aminoacetic Acid*

Observation Number	Aminoacetic Acid, Dose		Time			Number of Periods	Carbon Dioxide per Hr., Liters	Oxygen per Hr., Liters	Nitrogen Excretion per Hr.		Respiratory Quotient		Calories			
										Increase Over Control,						Increase, per Cent
	Gm.	Gm./Kg.	Start of Feeding	Start of First Period	End of Last Period				Total, Mg.	Mg.	Total	Non-N	Per Hr.	Per Kg., 24 Hr.	Increase	
5-24	5.0	1.89	9:03	10:05	2:55	5	1.520	1.604	88	47	0.948	0.970	7.873	71.57	9.75	15.8
5-23			9:00	10:15	11:45	2	1.208	1.360	41		0.888	0.907	6.594	61.82		
5-26	5.0	2.6	8:34	10:15	2:45	4	0.983	1.140	27	23	0.862	0.856	5.495	68.68	3.82	5.9
5-25			8:28	9:30	11:00	2	0.921	1.036	4		0.889	0.891	5.081	64.86		
5-27	5.0	2.4	8:28	10:10	1:48	4	1.085	1.216	....	....	0.893	.....	5.939 *	69.19	6.22	9.9
5-29			8:40	10:00	11:30	2	1.047	1.165	35	....	0.899	0.919	5.667	62.97		
7-24	4.0	1.67	9:28	11:10	11:45	1	1.145	1.253	37	26	0.914	0.915	6.148	61.69	6.37	11.5
7-23			9:25	10:55	12:05	2	0.943	1.102	11		0.855	0.859	5.348	55.32		
5-32	2.0 †	0.86 †	8:50	10:12	2:30	5	1.128	1.179	65	44	0.957	0.947	5.808	60.08	8.72	17.0
5-31			8:45	9:42	11:42	3	0.918	0.982	21		0.935	0.955	4.836	51.36		
7-16	2.5	1.0	9:40	11:50	1:00	2	1.254	1.343	56	26	0.934	0.951	6.591	63.99	—1.59	—2.4
7-17			9:25	10:40	11:50	2	1.474	1.489	30		0.990	1.017	7.432	65.58		
7-5	2.2	0.88	8:48	10:05	11:40	2	1.194	1.268	21	11	0.942	0.948	6.280	58.88	—0.29	—0.5
7-3			9:06	10:45	11:45	2	1.091	1.182	10		0.923	0.930	5.833	59.17		
5-39	2.0	0.47	8:32	9:58	2:55	3 ‡	2.294	2.528	97	22	0.907	0.928	12.303	69.97	—1.17	—1.6
5-38			8:36	9:56	11:56	2	2.251	2.484	75		0.906	0.928	12.15	71.14		

* Calculated on total respiratory quotient.

† Estimated to have been retained from a total ingestion of 1.72 Gm.

‡ A period from 10:43 to 11:28 a. m. omitted because of restlessness.

either a large rise lasting through about the middle of the second hour followed by a period in which the increase above the control level was not so striking or, more commonly, a steadily sustained heat production at well above the control level for at least five hours. Figures for individual hours are not given, but unless otherwise stated the figures in the table are averages of entire observations.

It is of interest that the greatest increases in heat production, 15.8 per cent and 17.0 per cent in observations 5-24 and 5-32 respectively, were found when the greatest increases in nitrogen excretion also took place, 47 and 44 mg. per hour respectively. In every instance in which aminoacetic acid was ingested, the nitrogen output rose by at least 20 mg. per hour, with a single exception (11 mg. in observation 7-5).

Phenylalanine and Tyrosine.—Phenylalanine (table 4) in doses of 0.4 to 2.0 Gm. per kilogram of body weight and tyrosine in the same dosage (table 5) caused no increase in heat production. In these two series of experiments, as in the aminoacetic acid studies, the amino acid observations were usually extended to five or six hours after ingestion, in order not to miss a delayed effect if one should occur. In 4 of eight observations with phenylalanine and in 2 of 4 with tyrosine the heat production was actually 5 per cent or more below the control level, suggesting that a depressant effect might be operating.

There was no significant increase in excretion of nitrogen after ingestion of tyrosine (table 5). After ingestion of phenylalanine (table 4), urinary nitrogen rose from 7 to 16 mg. per hour in 5 observations, and in 2 it was lower than in the control period. These results are in sharp contrast to the uniformly consistent increase in nitrogen excretion after ingestion of aminoacetic acid, despite the marked similarity in amounts of ingested nitrogen in the three series of observations. As noted in table 2 (except for observations 5-22 and 5-34), the amount of nitrogen ingested in the formula plus amino acid was within the same range, 0.48 to 1.10 Gm., whether aminoacetic acid or one of the aromatic amino acids was given. The failure of the infants to excrete any appreciable part of the nitrogen of ingested tyrosine and phenylalanine cannot be attributed to a failure of absorption of the amino acids. The excretion of large amounts of hydroxyphenyl derivatives, such as was described in reports on infants by Levine, Marples and Gordon,[6] was observed in 2 of the infants in the present series who had not received ascorbic acid (observations 6-2 and 7-14) and in an infant who had been given 10 to 20 mg. of ascorbic acid daily (5-41).[20]

Because of the finding of the authors cited that large doses of ascorbic acid can abolish the excretion of these derivatives, one series of observa-

20. Miss Eleanor Marples made the determinations of parahydroxyphenyl derivatives in the urine of these infants (see table 2, last column).

TABLE 4.—*Specific Dynamic Action of Phenylalanine*

Observation Number	Phenylalanine Dose		Start of Feeding	Start of First Period	End of Last Period	Number of Periods	Carbon Dioxide per Hr., Liters	Oxygen per Hr., Liters	Nitrogen Excretion per Hr.		Respiratory Quotient		Calories			
	Gm.	Gm./Kg.							Total, Mg.	Increase Over Control, Mg.	Total	Non-N	Per Hr.	Per Kg., 24 Hr.	Increase	Increase, per Cent
5-22	1.0	0.43	8:24	9:37	2:55	5	1.145	1.164	47	7	0.983	1.056	5.728	59.72	—3.71	—5.8
5-21			8:47	9:48	12:03	3	1.121	1.199	40		0.935	0.968	5.883	63.43		
5-34	1.0	0.45	8:36	10:08	2:04	3	1.086	1.224	46	8	0.887	0.914	5.985	64.31	—2.59	—3.9
5-33			8:40	10:21	11:51	3	1.109	1.247	38		0.889	0.907	6.049	66.90		
5-37	2.0	0.50	9:14	10:55	3:15	4	2.297	2.456	91	16	0.935	0.995	11.970	71.42	0.28	0.4
5-38			8:36	9:56	11:56	2	2.251	2.484	75		0.906	0.928	12.150	71.14		
5-41	2.2	0.80	9:15	10:30	1:55	5	1.328	1.428	54	—14	0.930	0.967	7.011	62.78	—3.36	—5.1
5-42			9:07	10:10	11:10	1	1.430	1.567	68		0.913	0.950	7.606	66.14		
6-2	5.8	2.0	8:50	11:00	12:30	3	1.186	1.310	36	2	0.905	0.927	6.385	53.02	—2.77	—5.0
6-3	5.8	1.93	9:17	11:10	12:40	3	1.327	1.421	42	7	0.934	0.968	6.957	55.66	—0.13	—0.2
6-1			8:46	10:30	11:30	2	1.281	1.310	34		0.978	1.011	6.509	55.79		
7-9	7.3	2.0	9:20	11:30	1:00	2	1.887	1.969	77	— 8	0.959	1.006	9.689	64.24	1.18	1.9
7-8			8:52	10:20	11:50	2	1.738	1.919	85		0.906	0.942	9.302	63.06		
7-14	5.6	2.0	9:13	10:45	11:45	2	1.394	1.341	92	14	1.039	1.202	6.599	56.36	—5.29	—8.6
7-13			9:08	10:25	11:25	2	1.500	1.399	78		1.072	1.206	7.013	61.65		

TABLE 5.—*Specific Dynamic Action of Tyrosine*

Observation Number	Tyrosine Dose		Time			Number of Periods	Carbon Dioxide per Hr., Liters	Oxygen per Hr., Liters	Nitrogen Excretion per Hr.		Respiratory Quotient		Calories			
	Gm.	Gm./Kg.	Start of Feeding	Start of First Period	End of Last Period				Total, Mg.	Increase Over Control, Mg.	Total	Non-N	Per Hr.	Per Kg., 24 Hr.	Increase	Increase, per Cent
5-35	1.8	0.47	9:44	11:11	3:15	3	2.129	2.250	64	2	0.946	0.975	11.080	69.98	2.66	4.0
5-36			8:47	10:55	12:30	3	2.104	2.205	62		0.954	0.984	10.884	67.32		
5-44	3.0	0.99	8:32	10:15	1:45	4	1.500	1.662	61	—5	0.903	0.930	7.989	63.02	—2.11	— 3.2
5-45			10:52	12:25	1:25	2	1.620	1.730	66		0.936	0.975	8.466	65.13		
7-1	4.4	2	9:00	1:15	2:45	2	0.913	0.952	11	1	0.960	0.972	4.732	51.86	—7.31	—12.4
7-4	4.9	2	9:03	10:35	12:05	3	1.045	1.142	11	1	0.915	0.922	5.620	54.87	—4.30	— 7.3
7-3			9:06	10:45	11:45	2	1.091	1.182	10		0.923	0.930	5.833	59.17		

tions (6-1, 6-2 and 6-3, table 4) was especially planned to test the effect of ascorbic acid, if any, on the specific dynamic action of an aromatic amino acid. On June 14, 1940 a control metabolic measurement was made on a premature infant who was spontaneously excreting the hydroxyphenyl derivatives in amounts equivalent to 597 mg. of tyrosine daily. Three days later phenylalanine in a dose of 5.8 Gm. (2 Gm. per kilogram of body weight) was given. An amount of derivatives equivalent to 964 mg. of tyrosine per twenty-four hours was excreted, and there was no specific dynamic action. Four days later, after the infant had received 700 mg. of ascorbic acid, the observation was repeated after administration of another 5.8 Gm. dose of phenylalanine. Despite the almost complete abolition of excretion of hydroxyphenyl derivatives (only 50 mg. per twenty-four hours), the ingested amino acid still had no calorigenic effect.

COMMENT

Many explanations have been advanced for the specific dynamic action of proteins and amino acids. It is universally agreed that work of digestion and absorption plays no part. It is also generally accepted that amino acids retained as constituents of body protein, either storage or structural, do not exert a specific dynamic action. The calorigenic effects have been attributed to the processes of deamination, conversion of ammonia to urea and excretion of the latter, and to the intermediary metabolism of the non-nitrogenous portions of the molecules. Lusk [1] gave greater importance to the reactions of the non-nitrogenous fragments, whereas Wilhelmj [21] emphasized the role of the nitrogenous portion to the extent that he believed that the extra heat production could best be expressed in proportion to "millimols of amino acid metabolized" measured by the excretion of extra nitrogen. Probably the best summary of the theories regarding specific dynamic action is that of Borsook,[2] who expressed the belief that it is due to the summation of effects from reactions of both the nitrogenous and the non-nitrogenous components of amino acids. He calculated that the extra calories produced by these two sets of reactions are roughly equal in a simple amino acid like alanine or aminoacetic acid. It seems reasonable to assume that in the metabolism of aromatic amino acids the non-nitrogenous fragments might contribute a relatively much greater part of whatever calorigenic effect occurs, for two reasons: First, phenylalanine and tyrosine contain only

21. (*a*) Wilhelmj, C. M., and Bollman, J. L.: The Specific Dynamic Action and Nitrogen Elimination Following Intravenous Administration of Various Amino Acids, J. Biol. Chem. **77**:127 (April) 1928. (*b*) Wilhelmj, C. M.: A Comparative Study of the Specific Dynamic Action of the Amino-Acids Alanine and Glycine, J. Nutrition **7**:431 (April) 1934; (*c*) The Specific Dynamic Action of Food, Physiol. Rev. **15**:202 (April) 1935.

about 7 or 8 per cent of nitrogen, in contrast to 18.6 per cent in the aminoacetic acid molecule; second, the metabolic processes involved in breaking down the derivatives containing the phenyl ring are far more complicated than those which take place in the conversion of alanine or aminoacetic acid to dextrose after deamination. While Wilhelmj [21a] stressed the part played by the nitrogenous fraction, he conceded the importance of the phenyl fraction of the phenylalanine molecule in heat production; indeed this must be recognized in view of the fact that he as well as Rapport and Beard [17] in animal experiments found that phenylalanine exerted a specific dynamic action two or three times as great as that of alanine in proportion to the extra nitrogen excreted. The substantial increases in heat production in animals following ingestion of tyrosine that were observed by Lusk [16] and by Rapport and Beard [17] were even more striking because they occurred when the excretion of nitrogen was increased slightly or not at all. A similar absence of increase in urinary nitrogen following ingestion of tyrosine in animals in which phenylalanine produced a definite increase has been reported by Butts, Dunn and Hallman [22] and by King and Rapport.[23] The latter gave tyrosine intravenously to dogs and observed a complete disappearance from the blood in five minutes, yet they could account for only a small percentage, in some observations for none at all, by increase of urinary nitrogen or phenol.

The occurrence of a specific dynamic effect, together with an increase in output of urinary nitrogen, in premature and in full term infants given aminoacetic acid is consistent with the idea that this substance is probably metabolized in the same way as in other subjects, i. e. that after deamination a good part of the nitrogen is excreted as urea and the nonnitrogenous fraction is converted into dextrose and probably oxidized.

The absence of specific dynamic action after ingestion of tyrosine and of phenylalanine may perhaps be explained as follows: The contribution of deamination and of urea formation would in any case be a small one, and in these observations practically no extra nitrogen was excreted. The energy-producing reactions of the deaminized fragments which ordinarily occur in adult animals were replaced in the infants observed by some other series of reactions. In those instances (for example, observations 5-41 and 6-2, table 2) in which parahydroxyphenyllactic acid and parahydroxyphenylpyruvic acid were excreted in large amounts, the conclusion would be justified that no appreciable calorigenic effect accompanied the excretion of these derivatives. In the

22. Butts, J. S.; Dunn, M. S., and Hallman, L. F.: Studies in Amino Acid Metabolism: IV. Metabolism of dl-Phenylalanine and dl-Tyrosine in the Normal Rat, J. Biol. Chem. **123**:711 (May) 1938.

23. King, F. B., and Rapport, D.: The Fate of Intravenously Injected Tyrosine, Am. J. Physiol. **103**:288 (Feb.) 1933.

cases in which such excretion was not observed, notably observation 6-3, which was identical with 6-2 except that the subject received also large doses of ascorbic acid, one may postulate that the deaminized fragments, or even the amino acid as such, were stored or built into the body structure. In 4 of 8 phenylalanine observations (table 4) and in 2 of 4 tyrosine observations (table 5) the heat production was actually diminished by at least 5 per cent after the ingestion of the amino acid. The possibility is not excluded that the retention of compounds containing the phenyl radical may have a depressant action.

SUMMARY AND CONCLUSIONS

Observations of the calorigenic effects of three amino acids were made on 10 premature and 3 full term infants, with the use of a respiration chamber indirect calorimeter of the open circuit type.

Aminoacetic acid in doses of 1 Gm. per kilogram of body weight or more always produced a significant increase in heat production, from 6 to 16 per cent above the control value.

In contrast, the resting metabolic rate following ingestion of phenylalanine and of tyrosine in doses of 0.4 to 2 Gm. per kilogram of body weight showed no rise above the control level, and in half of the observations there was actually a decrease of 5 per cent or more.

Excretion of nitrogen was significantly increased after ingestion of aminoacetic acid but was only slightly raised, when at all, after ingestion of the aromatic amino acids.

The conclusion is tentatively made that the energy-producing reactions which ordinarily contribute to the specific dynamic action of aminoacetic acid in adult animals occur also in infants but that in these subjects the aromatic amino acids may undergo a different series of reactions from those which normally occur in adult animals.

It was further demonstrated that the presence or absence in the urine of infants of deaminized intermediary products of aromatic amino acid metabolism did not influence the specific dynamic effect of these amino acids. Retention of these deaminized fragments or of the aromatic amino acids themselves may have taken place.

A depressant action of these aromatic compounds on the metabolic rate of premature infants has not been excluded.

Case Reports

CONGENITAL ABSENCE OF THE FOUR EXTREMITIES

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Ectromelia of the four extremities is one of the rarest of human congenital anomalies. A review of the literature reveals only 3 reported cases. Hare [1] in 1859, Price [2] in 1928 and Lereboullet, Benoist and Vanier in 1932 [3] have reported single cases. To our knowledge only 2 persons with this anomaly are living in the world today, a 61 year old Frenchman, Pierre Mathieu, in La Gacilly, Brittany,[4] and our patient. Several cases of absence of one or two extremities have been reported in the literature, but they are not within the scope of this paper.

REPORT OF A CASE

R. P. C., a boy of American-French parentage, aged 3 years at the time of this report, was delivered by one of us (R. E.) on Feb. 13, 1939, at full term. The mother's pregnancy was normal and her labor easy. The child breathed and cried spontaneously and weighed 4 pounds (1,842 Gm.). The father was 22 years old at the time of the patient's birth, and the mother was 18. He has a brother, aged 4½ years, and a sister, aged 2 years. The parents and these children are well. There is no history of miscarriages, tuberculosis, allergy, diabetes or cardiac, nervous, renal or venereal disease.

Physical examination at birth revealed a male infant with total absence of all four extremities, with the exception of a small flipper-like appendage attached loosely to the right hip region. This appendage was 8 by 4 by 4 cm. and consisted of soft fatty tissue and three hard, bony toelike structures having nails. There was no muscular control over this member. Small button-like buds of epithelial tissue were present at both shoulders and over the site of the left hip. The examination revealed no other abnormality except a high-arched palate.

The length of the body was 32 cm. (12½ inches). The circumference of the head was 32 cm. (12½ inches); of the thorax, 32 cm. (12½ inches); of the abdomen, 41 cm. (16 inches), and of the hips, 30 cm. (12 inches).

The child's subsequent health was good, and when he was 1 month old photographs (figs. 1 and 2) were taken and roentgenograms of all parts of the body

1. Hare: Tr. Path. Soc. London **10**:308, 1858-1859.
2. Price, M. D.: J. Indiana M. A. **21**:250 (June) 1928.
3. Lereboullet; Benoist, F., and Vanier, J.: Bull. Soc. de pédiat. de Paris **30**:439 (July) 1932.
4. Spot Mag. **2**:36 (Feb.) 1942.

were made (anteroposterior and lateral views). The report on the roentgenograms was as follows:

"There is no demonstrable pathologic condition in the skull or about the spine, ribs or pelvis. The chest and the heart are normal. There is total absence of

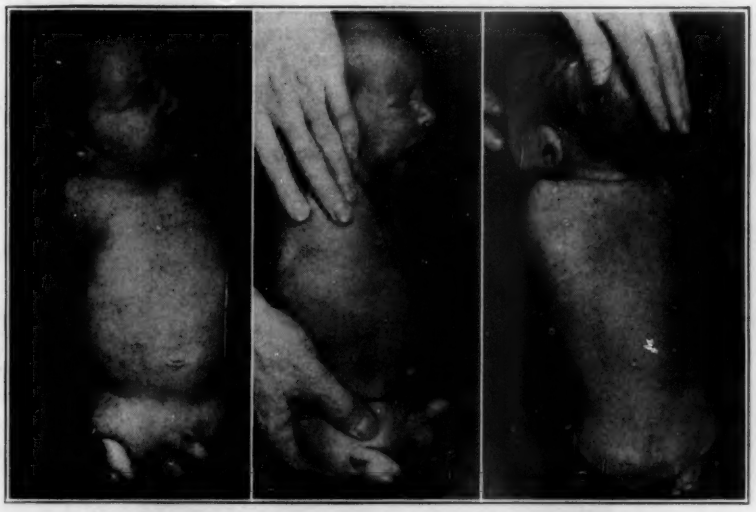

Fig. 1.—The patient at the age of 1 month.

Fig. 2.—Photograph showing excoriation of the buttocks due to ammoniacal urine and also the three-toe-like appendage.

both arms and of the left leg. Growing from the right thigh there appears to be a rudimentary foot (three small bones), measuring 8 by 4 by 4 cm."

The length of the body was 35 cm. (14 inches). The circumference of the head was 35 cm. (14 inches); of the chest, 36 cm. (14½ inches); of the abdomen, 46 cm. (18 inches), and of the hips, 32 cm. (12½ inches).

At this age the infant was able to roll over and away from painful stimuli, though the movements were not well coordinated.

The child's first year of life was a stormy one, requiring much medical care (which was unfortunate, since he was the son of a poor rice farmer living 8 miles [13 kilometers] from the nearest village). On March 29, 1939, after an infection of the upper respiratory tract, bronchopneumonia developed, but he recovered in five days after sulfapyridine therapy. On June 2 he and his brother became ill

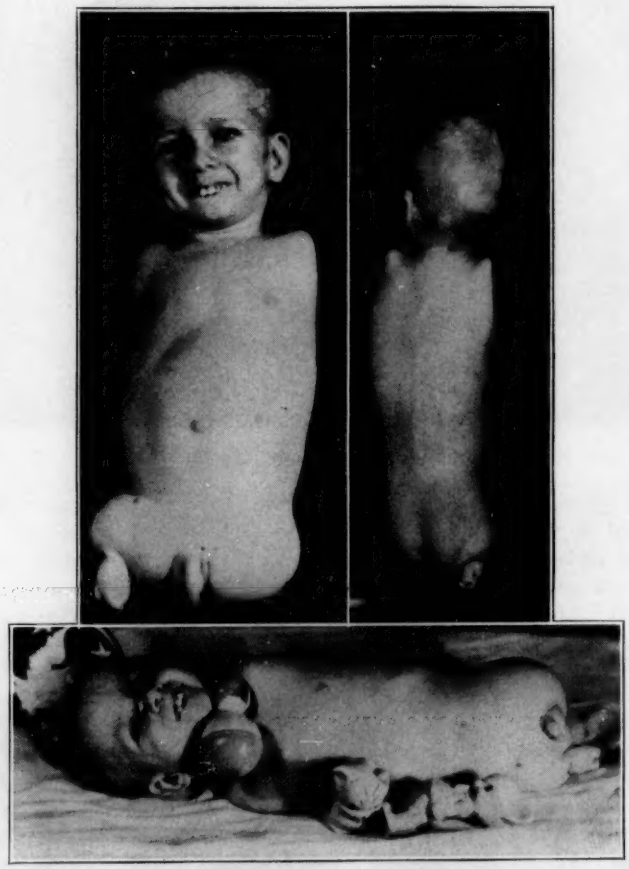

Fig. 3.—The patient at the age of 3 years. Note his ability to hold toys with his chin.

with diphtheria; both of them recovered (20,000 units of diphtheria antitoxin was given). On July 3 a mild attack of pertussis (contracted from his brother) began. He recovered in ten weeks (having been given three injections of 2 cc. of Lederle's detoxified pertussis antigen). On November 7 he again became ill, with severe scarlatina, for which he was given 6 units of scarlet fever antitoxin and several small transfusions of whole blood (jugular).

After this hectic first year of life, the child was placed in a nursing home and his condition was checked at regular monthly intervals. Immunizations for diphtheria, typhoid and smallpox were completed when he was 18 months of age.

Dentition was normal. The first lower central incisors appeared at 8 months, the first upper incisors at 11 months, the anterior molars and lateral lower incisors at 17 months, the canines at 26 months and the posterior molars at 31 months.

The senses of sight, hearing, smell, taste and touch have not been impaired. During the third month of life the infant smiled when played with. He laughed out loud at 5 months, at which time he was able to roll over and away from unpleasant surroundings at will. By the age of 1 year he was able to roll wherever he wished when placed on the floor. At 18 months he could say "dada," "mama" and "bye bye."

At the present time, at the age of 3 years (fig. 3), he weighs 18 pounds (8,290 Gm.). The circumference of the head is 46 cm. (18 inches); of the chest, 46.5 cm. (18.2 inches), and of the abdomen, 43 cm. (17 inches). The length of the body is 56 cm. (25½ inches).

Mental, emotional and physical development have been that of a normal child. The boy speaks simple words and knows child objects by name. He plays with toys, which he handles with his shoulders, chin, mouth and neck. He is able to move rapidly from place to place in his bed or on the floor by rolling over and over in a barrel-like fashion. He is unable to balance himself alone on his buttocks but can bounce around in a swing or small chair. One cannot understand or realize his abilities without actually seeing him perform. At present he is receiving special teaching for one hour daily.

COMMENT

Embryology.—"In the embryo of the fifth week the average length is between 2.5 and 5.5 mm. in size. The full number of primitive segments is attained by the end of the week. Characteristic features include the convex curvature of the back and the flexed head, the sharp bend at the level of the midbrain that bows the head is the cephalic flexure; the even more prominent curvature in the region of the future neck is the cervical flexure. Sense organs and branchial arches become prominent and the first arches bifurcate into primitive jaws. The trunk ends in a distinct tail and towards the end of the week (5th) *bud-like out-growths indicate the future upper and lower limbs.*"[5]

Etiology.—Any discussion of causative factors responsible for ectromelia of the extremities brings up many conjectures. Murphy and Bowes[6] have expressed the belief that improper diet and vitamin deficiencies may be responsible, "Although unproven by the present study, it could be within the realm of possibility that dietary deficiency, or the associated anemia, might be a predisposing factor." Toxemias of pregnancy and pelvic and uterine disease have also been incriminated.

5. Arey, L. B.: Developmental Anatomy, ed. 2, Philadelphia, W. B. Saunders Company, 1930, pp. 116-117.

6. Murphy, D. P., and Bowes, A. B.: Am. J. Obst. & Gynec. **37**:460 (March) 1939.

Greenhill [7] pointed out that in cases of placenta praevia the incidence of fetal monsters and deformities is 2.5 per cent, as compared with 0.9 per cent for all obstetric cases. His statistics are based on 4,446 cases of placenta praevia, representing approximately 4,000,000 obstetric cases.

The most plausible explanation of such a phenomenon, in view of the embryology of the human fetus, would seem to be that it is due to defective genes in either or both parents at the time of conception. All one can be certain of is that some pathologic or chemical change occurred at the 5 mm. stage of the fetus, thus preventing the normal development of the future limb buds.

A study of the reported cases in the literature and of the family history of this child gives no clue to the causation of this congenital anomaly.

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7. Greenhill, J. P., abstracted, Mod. Med. **7**:50 (May) 1939.

TYPHOID AT THE AGE OF FOURTEEN MONTHS

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Nowadays, thanks to the safeguarding of water supplies and the intelligent handling of food, typhoid has become a rare disease. Always the proportion of children having it has been extremely small; so a case of its occurrence now in a child under 2 years is almost a museum piece. Herewith is reported such a case, in which the diagnosis was proved by blood culture and stool examinations and the infection was, fortunately, traced to its unexpected source.

An idea of the degree of the occurrence of typhoid in children is afforded by a report of a careful study of 30,000 children seen in the service of Dr. Charles Hendee Smith in Bellevue Hospital, New York, between the years 1924 and 1938—a period of fifteen years (Kendig and Kirmse [1]). In this large group there were but 95 cases of typhoid in children under 12, an incidence of 0.3 per cent; of these, 39 occurred during a single epidemic. Some years there were no cases; 4 or 5 a year was the average. The patients with typhoid were mostly among the older children, only 1 being under 2 years; that patient was 14 months old, the same age as the patient whose case is here reported.

The symptoms of typhoid in children have always varied considerably from the clinical picture in adults, and it has usually been considered a mild disease, although statistics show that among infants and children the mortality remains relatively high, from 6 to 14 per cent (7 per cent in the children observed at Bellevue hospital). So variable is the picture in children that undoubtedly many cases are not discovered; and if physicians should become more alert to the possibility of typhoid and do more examinations of the blood and stools in cases of obscure intestinal infections, the incidence would undoubtedly rise.

Children with blood yielding typhoid bacilli on culture have been born during the course of typhoid in the mother, and there is considerable evidence of transmission of the disease through the placenta and through breast milk. The youngest reported sufferer from acquired typhoid was a baby of 21 days in China.[2] Its mother, 19 years old and

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Read before the staff of the Tompkins County Memorial Hospital and the Tompkins County Medical Society.

1. Kendig, E. L., Jr., and Kirmse, T. W.: Typhoid Fever in Childhood, Arch. Pediat. **57**:1-11 (Jan.) 1940.

2. Weech, A. A., and Chen, K. T.: Typhoid Fever: Report of a Case in an Infant Less Than One Month of Age, Am. J. Dis. Child. **38**:1044-1051 (Nov.) 1929.

well up to the time of her confinement, nursed her baby for six days. When it was 5 days old she became ill and proceeded to have typhoid. Although the baby showed no symptoms other than a failure to gain weight, blood cultures were made, which after two weeks were positive. There are 10 cases on record of typhoid in the fetus when the mother had the disease; the Widal reactions were positive and Bacillus typhosus was recovered from the organs. In Prague, so-called "typhoid city of Germany," of 1,530 patients with this disease 10, or 0.6 per cent, were under 2 years of age. According to Tupas and Quintos,[3] Holt reported no typhoid in children under 2 in 10,000 cases of acute illness in the New York Infant Asylum, and the New York Foundling Hospital had never reported an instance. In the Philippine General Hospital, out of 19,037 patients observed in ten years, there were 223 with typhoid, *none* under 2 years of age.

According to Holt,[4] in over 14,000 patients admitted to the Babies' Hospital, New York, in a period of thirteen years, there were but 11 patients with typhoid under 2 years of age and but 5 aged 1 year or under, the youngest being 8 months. From the Children's Hospital in Philadelphia Griffith reported 45 cases in which typhoid occurred in children under 2 years old and 9 in children under 1 year.

The clinical picture of typhoid in infancy and childhood varies from the pattern which we usually associate with this disease. Except when one is looking for it, as during an epidemic or after a known exposure, the diagnosis is often not made early enough to get a positive blood culture. To refer again to the patients studied at Bellevue Hospital, typhoid was not even suspected at first in 28 of the 95 cases. The most common wrong diagnoses were: acute tonsillitis, lobar pneumonia, tuberculosis and rheumatic heart disease. Eventually all but 2 of these children had positive Widal reactions, but of the 69 blood cultures taken, only 22 were positive for typhoid.

Roseola was recorded in about 65 per cent of these cases, although other reports give an incidence as low as 7 per cent. On the basis of these observations, the incidence of palpable spleen is extremely variable; so is the pulse rate, there being no marked slowing in relation to the temperature. Diarrhea is usually only of two or three days' duration. The largest number of positive stools are found in the second week. In 10 of the 95 cases observed at Bellevue Hospital B. typhosus was at

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3. Tupas, A. V., and Quintos, F. N.: Typhoid Fever in Children, J. Philippine Islands M. A. **16**:545-553 (Sept.) 1936.

4. Holt, L. E., Jr., and McIntosh, R.: Holt's Diseases of Infancy and Childhood, ed. 10, New York, D. Appleton and Company, 1933, pp. 1148-1152.

no time recovered from the stools. The average duration of fever was eighteen days. Relapses occurred in 12 per cent of the cases, the average time being thirteen days after defervescence. Intestinal hemorrhage occurred in 4 per cent of the cases.

A wide variation prevails in the blood counts, but the impression is gained from a study of several groups of patients that leukocytosis occurs at the beginning of the attack and persists until the invasion of the blood stream, when leukopenia occurs. Some children never show leukopenia, but all who are severely infected do.

REPORT OF A CASE

Margaret M., an unusually healthy and well ordered baby of 14 months, with two healthy older bothers and with no illness in the household or in the neighborhood, was thought by her mother to be feverish, although she was lively and happy and showed no sign of illness. The mother was a graduate nurse. Despite the absence of symptoms, the temperature for two days went as high as 102.4 F., and she was brought to my office. At that time the temperature was 102 F. by rectum, but a careful physical examination was of no help in the diagnosis. A specimen of urine obtained three hours later showed nothing abnormal except a few scattered leukocytes and two or three clumps of 3 or 4 white cells. In the absence of any other indications small doses of sulfathiazole (2-[paraaminobenzenesulfonamido]-thiazole), 1 Gm. daily, were given for two days. The temperature kept going up, and further specimens of urine being normal except for bacteria, pyelocystitis was abandoned as a diagnosis and the administration of sulfathiazole was discontinued. Despite absence of enlarged postcervical glands and a perfectly normal throat, a tentative diagnosis of rubella was made.

Two days later several small glands were palpated in each axilla (none elsewhere). Otherwise physical examination still gave negative results, and infectious mononucleosis arose to compete with German measles as the best wrorg diagnosis! The white cell count was 14,900, with polymorphonuclear leukocytes at 21 per cent. Still the child did not appear ill, even with a temperature which had mounted to over 104 F. She was removed to the hospital, not because she appeared very ill but largely because of two facts: The family carried hospital insurance, and the mother was expecting another baby in a few weeks and had her hands full without illness to complicate the situation.

On December 5, the day she was admitted to the hospital, the urine was normal except for a 4 plus bacteria count. This was the blood picture: hemoglobin 68 per cent, red cells 3,890,000 and white cells 11,800 (polymorphonuclears 38 per cent, lymphocytes 58 per cent and mononuclears 4 per cent). A few smudges were seen. One day later the blood count was approximately the same, the hemoglobin content having risen to 73 per cent.

Although the chest was clear and the child had no cough, a roentgenogram was taken; it showed no pathologic condition.

By December 8 she appeared to be getting sicker. The temperature stayed between 104 and 105 F.; the pulse rate was seldom below 160, and the stools had become dark and liquid. Axillary glands were definitely palpable; the spleen was not felt, and there were no rose spots. The blood picture had changed in two days to this: hemoglobin 53 per cent, red cells 3,490,000 and white cells 7,600 (polymorphonuclears 47 per cent, lymphocytes 51 per cent and mononuclears 2 per cent). There were a few smudges. Blood was taken for agglutinations and for culture and was typed in the event that transfusions became necessary. Throat culture showed nothing of importance. A stool was sent to the laboratory. At this time two small suboccipital glands were felt, in addition to those in the axillas.

In due time the laboratory reported that agglutinations were negative for all organisms of the typhoid group and for those of undulant fever and that the heterophile antibody test failed to show evidence of mononucleosis. But there was a growth on the blood culture which proved to be typhoid bacilli, and the examination of the first stool showed many of these bacilli.

The temperature rose to nearly 105 F. every day, with one morning remission, until the sixth day, when it stayed up. On the eleventh day lysis began, and it continued typically until the nineteenth hospital day of illness, after which the temperature never rose above normal.

Throughout the course of the disease there were never any rose spots nor was the spleen palpable. The enlargement of the axillary glands was not explained; it persisted until about two weeks after the child's discharge from the hospital, at which time the glands could no longer be felt.

There was a definite odor to the child during the height of her illness which some who had had experience with typhoid said was the typhoid odor. Such an observation after the diagnosis was established would of course be of no importance; but the mother, who had cared for patients with typhoid during her years as a trained nurse, twice remarked about this odor before the diagnosis had been made.

For a week at the height of the disease the child seemed quite toxic and prostrated and was somewhat drowsy even after administration of camphorated tincture of opium U. S. P., given during a few days of loose bowel movements, had been discontinued; she never vomited and ate pretty well of a high calory diet, mostly without milk. Her blood picture improved rapidly as she got better, and there was neither relapse nor hemorrhage. The last blood count, on January 2, five days before discharge from the hospital, was: hemoglobin 63 per cent, red cells 4,160,000 and white cells 6,300 (polymorphonuclears 11 per cent, lymphocytes 87 per cent and mononuclears 2 per cent). When she left the hospital, the stools were free of typhoid bacilli, but on the third examination after her discharge bacteria were again recovered, although in small numbers. The child was ill approximately five weeks.

This child had not been out of town or eaten away from home, and no one among her associates had been ill. There were no cases of typhoid in town. Inquiry revealed that the mother had had typhoid thirty years previously. Since then, however, she had practiced her profession of nursing, had married and gone through three successful pregnancies and had always been well.

Stools of both parents were examined for typhoid bacilli; the father's did not contain any, but the culture of the mother's yielded a luxuriant growth.

An interesting observation from the mother was that on at least two occasions she had found this child in the bathroom dabbling her hands in the water of the toilet.

SUMMARY

The incidence of typhoid in childhood is briefly reviewed.

A case of typhoid in a child of 14 months is presented. The source of the infection was found to be the mother, who after having had the disease thirty years previously still had the organisms in her stools.

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ENTEROGENOUS PULMONARY CYST

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AND
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The purpose of this paper is the presentation and discussion of 2 unusual cases of cyst of the lung. The second case suggests a new cause of spontaneous pneumothorax in infants. Insofar as we have been able to determine, no similar case has been reported in modern literature. The attempted correlation of the embryologic, pathologic and clinical relationship was, to us at least, interesting.

We believe the cysts in these 2 cases arose from anlages of the primitive gut. At necropsy they were not seen to be in any way connected with the gastrointestinal tract. The cysts were not the usual small islands of aberrant intestinal or pancreatic tissue sometimes found along the esophagus but were definite hollow, spherical, organoid tissues, isolated at the periphery of the lung. Although they were almost identical in their gross and histologic pathologic aspects, they showed some decided differences in their clinical manifestations. The causes of these differences, we think, were purely physical and were dependent on two different types of bronchocystic patencies.

REPORT OF CASES

CASE 1.—*History.*—The patient was delivered by a classic cesarean section at full term. No abnormalities were noticed at birth. Although the baby took feedings well, he failed to show a normal gain in weight. At the age of 3 weeks, he began to have a wheezing snore during sleep. On several occasions he passed black stools and expelled bloody sputum or vomitus.

When he was 9 weeks old, intermittent attacks of a gagging cough and rapid respiration associated with dyspnea began. These symptoms became so frequent and so severe that the patient was brought to the hospital. Several weeks prior to his admission, the mother had noticed a gradual but progressive enlargement of the right side of the chest.

All the other history was essentially irrelevant.

Physical Examination.—The patient was a 9 week old white boy who was pale, sickly, small, poorly nourished and dyspneic. His temperature was 99.8 F., his pulse rate 140 and his respiratory rate 40.

From the Department of Pathology, Hurley Hospital.

The significant findings were limited to the chest and to the abdomen. The right side of the chest showed anterior bulging from the clavicle to the ninth rib. The most prominent part of this enlargement was along the anterior axillary line. The entire right side of the chest showed a marked impairment of respiratory excursion, with dulness to percussion and absence of breath sounds.

The left side of the chest showed good excursion, resonance on percussion and a few scattered coarse inspiratory rales.

The left border of cardiac dulness extended to the anterior axillary line. The cardiac rhythm was normal, the rate was fast and no adventitious sounds were heard.

The abdomen was tense and distended, and no abdominal masses could be palpated.

Laboratory Examination.—The white blood cell count was 25,000, with polymorphonuclear cells 76 per cent and lymphocytes 24 per cent; the nuclear index

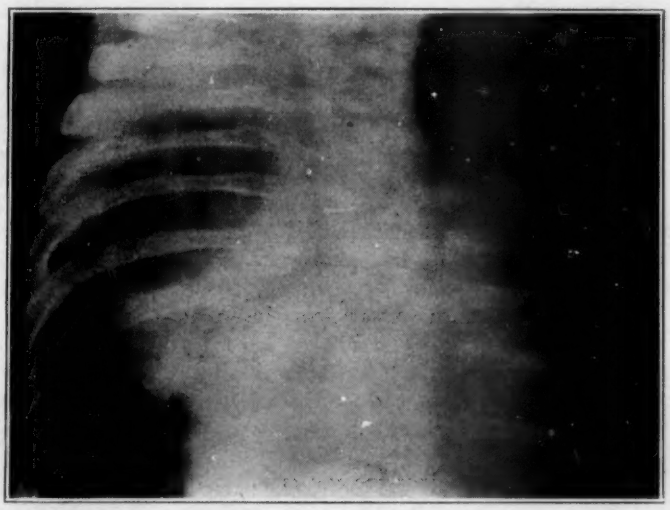

Fig. 1 (case 1).—Roentgenogram of chest.

was 3.8. Examination of aspirated fluid revealed much black, free pigment and a few pus cells; routine cultures gave negative results.

Roentgenologic Examination.—A roentgenogram taken on the patient's admission showed in the upper lobe of the right lung an area of decreased density which was devoid of normal lung markings and which was surrounded by an area of increased density. Irregular fine lines wandered through the area of decreased density. The medial portions of the middle and lower lobes and a small area on one side of the lower lobe appeared to be atelectatic. The roentgenologic report was that there was a multilocular cyst of the right lung with accompanying atelectasis.

A second film, taken one day later and seven days before the child's death, showed a considerable increase in the size of the cyst with still further compression of the lower and middle lobes.

Progress.—The attacks of dyspnea and cyanosis became progressively more severe and prolonged. Feedings were taken poorly, and there were frequent attacks of gagging and coughing which produced a considerable amount of brown mucus.

All stools were dark brown. The temperature varied from 99 to 105.8 F., the respiratory rate from 30 to 92 per minute and the pulse rate from 130 to 170 per minute. Aspiration of the chest in the right fourth interspace yielded 15 cc. of thick fluid which had the appearance of old blood.

The patient died on the eighth day in the hospital at the age of 10 weeks, after a progressively downhill course.

Necropsy.—Gross Examination: The body was that of a poorly nourished, dehydrated white boy weighing 4,100 Gm.

There was an anterolateral bulging of the right side of the chest, extending from the clavicle to the ninth rib. A cystic mass completely filled the upper two thirds of the right side of the thoracic cavity. It was anterior and lateral to an atelectatic lung. It was firmly adherent to the parietal pleura and one-third submerged in lung.

The apex of the heart was at the sixth interspace at the anterior axillary line. The mediastinal structures were displaced to the left. The thoracic and abdominal viscera were removed en masse.

When the right thoracic viscera were dissected, two distinct, adjacent cystic masses were found. The superior one measured 3 by 5 by 4 cm. and was composed of multiple, incompletely loculated cysts which contained approximately 60 cc. of thick brownish black mucus. The wall averaged 7 mm. in thickness and was composed of an outer, serosal layer which was covered with dense adhesions and an inner, mucosal layer which was thick and of a pink to brownish black color with scattered areas of hemorrhage. The right upper lobe bronchus extended into this mass, where it lost its cartilaginous structure and assumed the appearance of a thin tube of mucous membrane. This was penetrated by minute openings through which the contents of the cyst could be expressed.

The inferior cyst measured 7 by 4 cm. and was adherent to the superior mass, with which it did not communicate. The structure of this cyst was similar to the other except that it had no communication with any of the bronchi or other thoracic viscera. The trachea and the major bronchi of both sides were plugged with mucus and a viscid brownish black material.

Just anterior to the hilus there was a small mass of soft black tissue which represented the upper and middle lobes of the lung. An atelectatic lobe was displaced anteriorly and medially.

The left lung showed patchy atelectasis. The heart was grossly normal. The diaphragm was normal and intact. The abdominal viscera showed no significant changes or abnormalities, and the gastrointestinal tract was normal throughout.

Microscopic Examination: Multiple sections through both cystic masses showed a well formed wall composed of three layers of smooth muscle, a thickened, fibrotic serosa and a well formed mucosa, the cellular elements and structures of which were typical of gastric mucosa. Some areas of the mucosa were hyperplastic and catarrhal, while others showed superficial ulceration. Many pink acid cells were present.

One section of the superior cyst revealed a focal submucosal acute purulent inflammatory process. Sections through the black mass representing the upper lobe showed it to be extremely atelectatic and filled with phagocytosed blood pigments and large amounts of free granular black pigment. The lower and middle lobes of the right lung showed patchy atelectasis, and many of the alveoli were filled with free black pigment, pus cells and debris. The bronchioles were involved

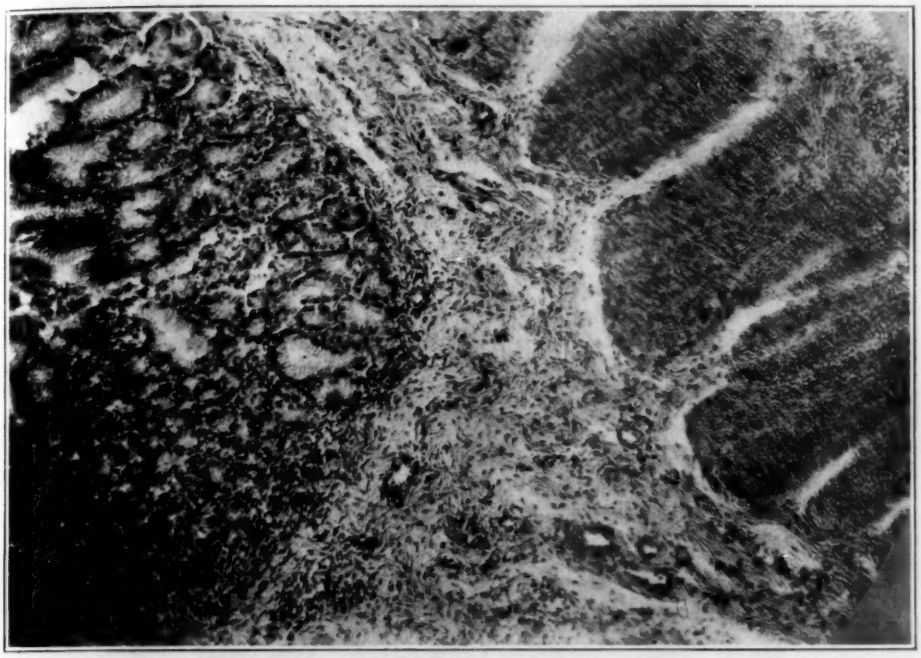

Fig. 2 (case 1).—Microscopic section of cyst (hematoxylin and eosin; × 100).

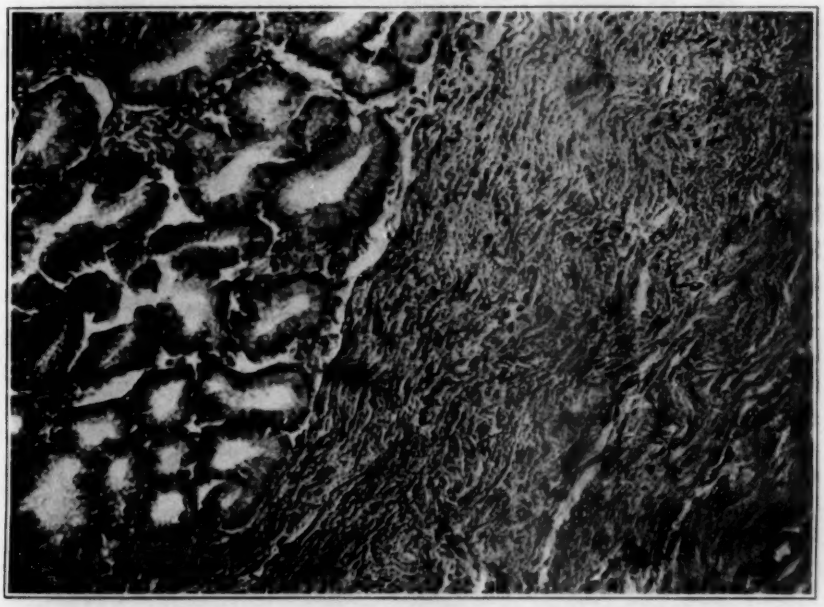

Fig. 3 (case 1).—Microscopic section of cyst (hematoxylin and eosin; × 160).

in an acute inflammatory process, and in all areas they showed deformity by pressure. The left lung contained areas of patchy atelectasis with compensatory emphysema. Many of the alveoli and bronchioles were filled with the same black pigment. Sections about the hili of both lungs revealed an acute purulent bronchitis and early bronchopneumonia.

Sections of the remainder of the thoracic and abdominal viscera failed to reveal any additional pathologic changes of importance.

CASE 2.—*History.*—The patient, the second child of healthy parents, was delivered normally and spontaneously. He had an uneventful postnatal course until the age of 6 weeks, when there suddenly developed profound respiratory difficulty accompanied by marked cyanosis. He was placed in a hospital, and a roentgenologic diagnosis of pneumothorax on the right side was made. He was put in an oxygen

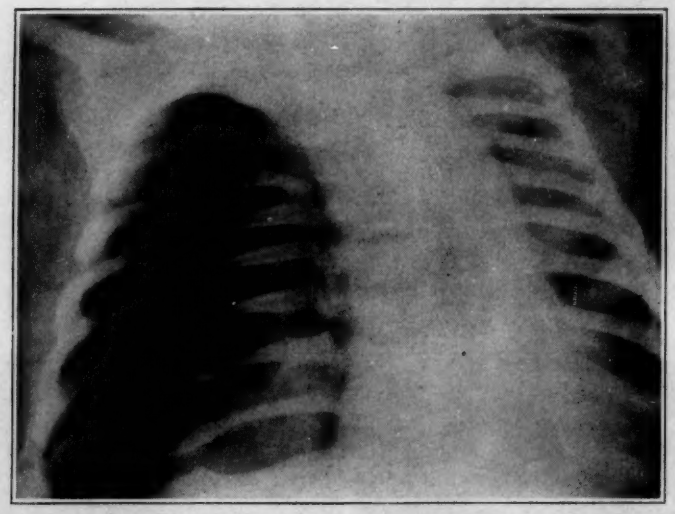

Fig. 4 (case 2).—Roentgenogram of chest.

tent and responded so well that he was discharged on the sixth hospital day in what appeared to be excellent condition.

Two weeks later he had another attack of cyanosis and dyspnea and was again placed in the hospital. In this attack he would occasionally choke and by coughing would raise moderate amounts of viscid mucus.

Physical Examination.—The patient was an 8 week old breast-fed infant, well and normally developed, breathing rapidly and with difficulty and showing definite signs of cyanosis. His temperature was 100 F., his pulse rate 120 and his respiratory rate 40.

The significant physical findings were limited to the chest. The right side of the chest was highly tympanitic to percussion, and the breath and voice sounds were faint and distant. The left side was apparently normal. The apex beat was approximately 2 cm. to the left of the anterior axillary line.

Roentgenologic Examination.—The roentgenologist reported a definite, rather large, right-sided pneumothorax with a small area of decreased density in the

midclavicular line at the level of the third rib anteriorly, which suggested a pulmonary cyst. The heart and mediastinal shadows were pushed far over to the left.

The second roentgenologic report, made five days after admission, mentioned a decrease in the size of the pneumothorax. A third report, made fifteen days after admission, pointed out a still further reduction of the pneumothorax and a persistence of the area of decreased density.

Progress.—The patient was placed in an oxygen tent but continued to be cyanotic and dyspneic until the second day, when 65 cc. of air was aspirated from the right pleural cavity. After this aspiration, his color became good and his respirations easier.

Fig. 5 (case 2).—Gross specimen containing the cyst.

On the following day he again became cyanotic and dyspneic, and 100 cc. of air was aspirated. His breathing and color were immediately improved and remained so until the sixth hospital day, when the aforementioned symptoms suddenly returned. A needle was again introduced into his right pleural cavity, and the intrapleural pressure at this time was so great that it forced the plunger of the attached syringe backward until approximately 50 cc. of air was aspirated. In all, 175 cc. of air was removed at this time. The aspirations again relieved the symptoms and the child remained in fair condition until the twenty-second hospital day, when he again became cyanotic and dyspneic, had an abrupt rise in temperature to 105 F. and died soon afterward.

Necropsy.—Gross Examination: The patient was a well and normally developed 11 week old white boy weighing 5,850 Gm. External examination revealed an

essentially normal condition except for cyanosis of the lips and finger nails and thick mucous discharge in both nostrils. An under-water opening of the chest revealed the presence of air in the right pleural cavity. The right pleural space contained a collapsed lung which was firmly bound to the mediastinum and closely adherent in the upper part of the thorax to the posterior chest wall and vertebrae.

Fig. 6 (case 2).—Microscopic section of cyst (hematoxylin and eosin; × 100). Note the pancreatic tissue in the lower right corner.

All of the mediastinal structures were to the left of the midline. The wall of the right side of the chest showed no evidence of perforation, laceration or dehiscence to the outside. The left lung was grossly normal. The diaphragm and gastrointestinal tract were normal throughout.

An under-water test for a bronchopleural fistula gave negative results. Examination of the right lung showed on its posterior surface a firm white mass of tissue

measuring 3 by 2 by 2 cm. which was partially submerged in the pulmonary parenchyma and over which the pleura was not intact. When the mass was opened under water, bubbles of air escaped from its central portion. Section showed it to be a well differentiated hollow spherical structure having a muscular wall lined with mucous membrane. Approximately one third of it was buried in the paren-

Fig. 7 (case 2).—Microscopic section of cyst (hematoxylin and eosin; × 160).

chyma of the superior and middle lobes, and the adjacent lung tissue was blackish red. No cystic-pleural patency could be demonstrated by very heavy pressure with a large syringe in the trachea.

Microscopic Examination.—Sections through the tumor mass revealed two histologic pictures. The inferior portion was typical of duodenum and contained accessory pancreatic tissue in the muscular wall. The pancreatic ducts were well

developed, and islands of Langerhans were present but scanty in number. The upper portion of the tumor was typical gastric mucosa and wall. There were various areas of hyperplasia and catarrh of the mucous membrane. This cyst was a remarkable imitation of the pyloric area of the stomach. Brunner's glands were not found. The right lung was atelectatic in its entirety. No bronchocystic patency could be found. The left lung showed chronic stasis and a moderate alveolar fibrosis.

The observations on sections of the remainder of the necropsy material were irrelevant.

Summary.—A cyanotic boy of 11 weeks, well nourished and well developed, presented a muscular cyst of the posterior portion of the right lung. There was a severe mediastinal shift to the left with total atelectasis of the right lung and pneumothorax. There was no remaining evidence of a cystic-bronchial or cystic-pleural connection. The cyst at necropsy was much smaller than the area of decreased density in the roentgenograms. The immediate cause of death is believed to have been a sudden further mediastinal shift.

COMMENT

In our perusal of the literature, we were able to find citations of only 5 intrathoracic cysts shown by histologic examination to be made up of true gastric or intestinal tissue. Of these 5 cysts, 3 were definitely due to diverticulations of some part of the gastrointestinal tract and 2 showed no direct connection with any other viscera. None of these cysts communicated with the bronchi or were accompanied by a pneumothorax.

Because the 2 cysts we are reporting were located at the periphery of the bronchial tree, because 1 of them was attached to and definitely communicated with a bronchus and the other showed evidence of recent bronchocysticopleural patency and because they were in no way attached to the gastrointestinal tract or diaphragm, it seems to us that the most logical explanation of their presence is that during the third or fourth week of fetal life a few cells which retained their enterogenous potentialities were pinched off from the primitive gut and were carried to their present location by the outgrowing tracheal bud to which they were attached.

In case 1, an explanation of the clinical symptoms in the light of the pathologic observations is not difficult. The progressive character of the symptoms resulted from an accumulation of secretions in the cysts and a slow but continuous enlargement of the cysts with encroachment on the adjacent lung. The respiratory difficulties were caused by compression of the thoracic contents and an overflow of secretions from the superior cyst into the bronchial tree. The blood-stained secretions from the superior cyst also account for the sputum and discolored stools. The terminal symptoms were those of a superimposed inflammatory process.

In case 2, the correlation of the clinical and pathologic observations is not so easy. The sudden attacks of dyspnea and cyanosis were obviously due to a rapidly developing pneumothorax and mediastinal shift. The pronounced relief following each aspiration verifies this conclusion. A positive proof of the cause of the pneumothorax cannot be advanced. However, we offer the following explanation as the most probable.

That there had been some type of bronchocystic patency during life is supported by two known facts. First, although the cyst was completely collapsed at necropsy, it still contained a small amount of air. Second, the area of decreased density shown in the roentgenograms was approximately twice the size of the cyst found at necropsy. The possibility of a former pleurocystic patency is suggested by the frayed nature of the pericystic pleura at the upper pole of the cyst. It seems quite possible that if the bronchocystic connections were narrow and entered the cyst wall at an angle, a one way valve effect would be established. Then the cyst, being an expansible organ, would gradually increase in size and build up a progressively increasing intracystic pressure. This increased pressure, along with the stretching of the cyst wall, would open a potential pleurocystic patency and the pneumothorax would result. Certainly some type of one way valve patency must have been present to cause the extremely high intrathoracic pressure present at the third aspiration of air. The escape of the air into the pleural cavity would result in a collapse of the cyst and the lung, and this collapse would immediately close all communications between the bronchial and pleural spaces until the pneumothorax was partially relieved. If the pneumothorax persisted for some time, the patencies would become so firmly closed that they could not be demonstrated at a necropsy done several hours following the occlusion.

This, of course, is offered only as a theory to explain the cause of the pneumothorax and our inability to demonstrate any bronchopleural communications at necropsy.

Dr. Lafon Jones, Chief of Pediatrics at Hurley Hospital, and Dr. F. B. Miner, Chief of Pediatrics at St. Joseph Hospital, permitted us to use these cases.

Hurley Hospital.

Progress in Pediatrics

DESIGN CHARACTERISTICS OF DOUBLE CUBICLE SYSTEM FOR PROTECTING BABIES IN NURSERIES

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THEORY

Maintaining infants in large groups, as in nurseries and in homes for foundlings, creates the problem of cross infection. One solution of this problem involves isolation of infants one from the other, so that vector lines can be reduced to a few which are well defined. Infants grouped together in a room and attended by various persons concerned with their care and maintenance are the focus of many complex and interacting vector lines. For purposes of convenience the vectors can be divided into two groups: air-borne vectors and contact vectors. Actually, however, it should be noted that such a division is a matter of convenience, as vectors are interchangeable.

Infants may be isolated from each other by surrounding them with mechanical barriers in the form of a cubicle, which must be so designed that the baby is easily handled and observed. Furthermore, unless the mother is isolated with the child added protection must be set up in the form of apparatus for showing the baby. This report is concerned with a cubicle of special design, called for convenience a "double cubicle" or sometimes the "Reyniers cubicle." The term double cubicle is preferred.

Elimination of Cross Infection in Baby Populations, Particularly Air-Borne Infections, by the Use of a Double Cubicle.—Air-borne vectors are dust, droplets, droplet nuclei and spores. The vector lines involved in air-borne infections are shown in figure 1, together with a scheme for protection against these lines by the use of the double cubicle. Briefly, this cubicle functions on the idea that the paths of infective particles are flowing. Thus, air-borne routes of infection are eliminated by controlling the direction of air flow. The cubicle is an air-tight chamber divided into two smaller chambers, a baby space and a nurse space, by a partition which contains a sliding delivery window. Subjects to be isolated are placed in the baby space, and all handling of the subject is done through the delivery window under aseptic conditions. To prevent air-borne vectors from penetrating the baby space, each chamber

is separately supplied with filtered air; moreover, between baby space and nurse space there is a difference in air pressure sufficiently great so that the air flow through the open delivery window is always toward the nurse space.

Elimination of Contact Infection in Baby Populations by the Double Cubicle.—The baby in a double cubicle is protected against contact infection by the flexible sheath barriers (gowns, mask and gloves) assumed by the attendants (nurse, doctor, etc.) before they open the delivery window. The gown is always left in the nurse space of the cubicle in which it is used. The attendant is already masked, and rubber gloves are unnecessary if the hands are scrubbed and dipped in an antiseptic solution before a baby is handled. Only the arms of the

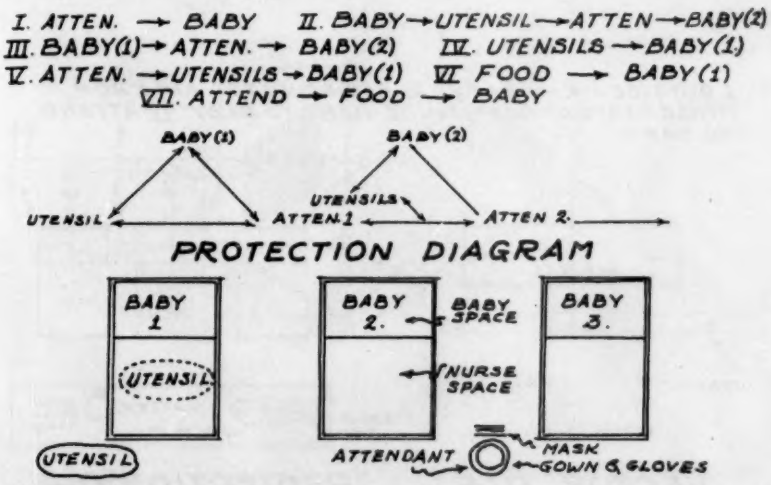

Fig. 1.—Diagram of air-borne vectors, vector lines and method of protection by ventilation barriers.

attendant enter the baby space. The gown is merely a sheath which can be shed when it is contaminated. Vectors, vector lines and the protection against contact infection are illustrated in figure 2.

Elimination of External Noises.—Each baby isolated in a cubicle enjoys a quiet environment undisturbed by external noises of the nursery. This assures a maximum of rest. Dr. Rosenstern, of the Cradle, Evanston, Ill., reports an increased gain in weight by babies housed in this manner.[1] He also raises a question as to whether stimulation of the baby occasioned by noises is not desirable. This, however, seems to be a moot question for the moment.

1. Sauer, L. W.; Minsk, L. D., and Rosenstern, I.: The Control of Cross Infection of the Respiratory Tract in a Nursery for Young Infants: A Preliminary Report, J. A. M. A. **118**:1271 (April 11) 1942.

Individual Air Requirements.—It is possible to change the humidity and temperature of one cubicle without affecting others. For instance, the humidity and temperature requirements for prematurely born babies are different from those for babies born at term. In the double cubicle only the baby space need be regulated, and the attendant may be permitted any degree of comfort. Any of the standard devices for regulating humidity and temperature may be employed.

In summary, then, the operating principles of the double cubicle are as follows:

1. Isolation of each baby in an air-tight, sound-proof, individually ventilated cubicle.

2. Provision for each baby of a filtered, germ-free and dust-free air supply.

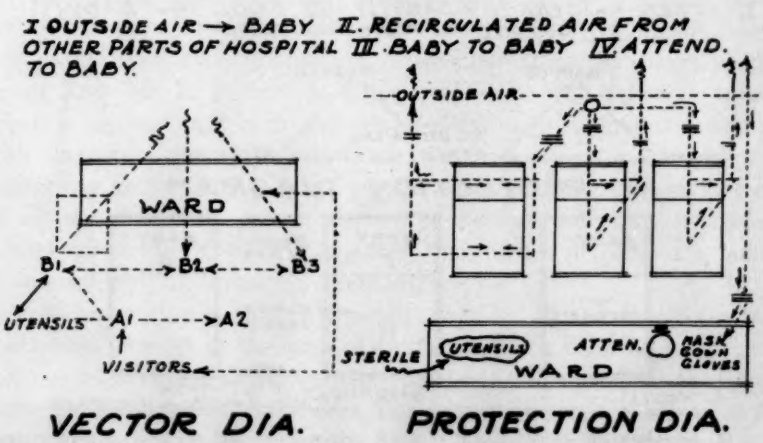

Fig. 2.—Diagram of contact vectors, vector lines and method of protection by mechanical barriers.

3. Maintenance of a difference in air pressure between the baby space and the nurse space, so that the isolated baby may be handled or fed against a flow of air which prevents outside contaminated air from entering the baby space.

4. Use of an aseptic technic in handling each baby to prevent the transmission of contact vectors from cubicle to cubicle or from nurse to baby.

The advantages of the double cubicle are as follows:

1. Each baby is assured a quiet, noninfective environment which can be adjusted to individual requirements of temperature and humidity without affecting the attendant.

2. If a baby becomes infected, the infection is localized in the cubicle.

3. Once constructed, the cubicle has no maintenance cost, because no replacements are necessary.

4. Mechanical barriers are constant in that they work all of the time.

5. Insect vectors are eliminated.

6. The attendant is separated from the baby by the inner barrier until properly disinfected.

7. The steps in an aseptic procedure are mechanized.

If the cubicles are located in a hospital of standard design, the baby is taken to the mother, where it may be infected. This danger can be eliminated, of course, by isolation of the mother and the baby together, but such a design system is unusual. The problem in the hospital is

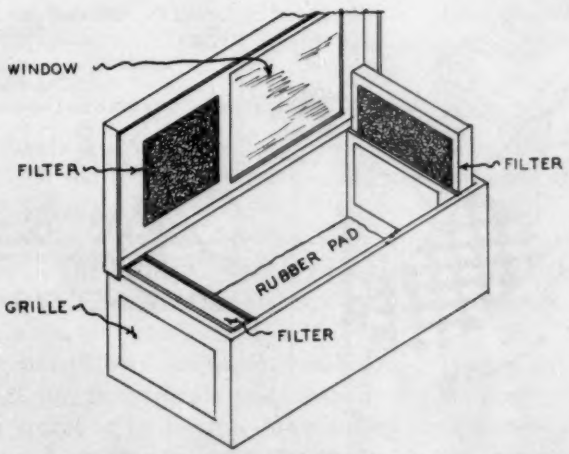

Fig. 3.—Box for moving baby from cubicle to mother and back to cubicle.

to prevent the spread of infection. Therefore, when the baby is removed from the cubicle it is first placed in a box of special design (fig. 3) which is constructed of metal and which has a filter at either end. The box is not opened until the baby is given to the mother. When it is returned to the nursery the outside surface may be sterilized. At no point is one baby in contact with another; hence cross infection from this source is eliminated.

CONSTRUCTION

Cubicles should be constructed as individual units independent of the walls, ceiling and floor of a room. This is true in either a new or an old building except that in new buildings the services and ducts may be properly arranged. Enough glass must be included in the front of the cubicle to allow full view of the baby. My associates and I believe that a nurse or attendant works best sitting, although in the cubicles

built for the Cradle in Evanston the attendants work in a standing position. The cubicle shown in figure 4 illustrates the general design, in which the nurse sits at her work. In this type the baby space is built as a separate unit and placed in the cubicle. The floor of the baby space forms the bed on which the baby rests. The baby is placed in its space through a crib door which swings down, and it is handled through a delivery door which swings up so that the arms may be inserted. An outward swinging door in the front of the cubicle allows access to the nurse space.

Cubicle walls should be constructed of metal sheets framed on angle iron construction. Welded joints are preferable, because they are air-

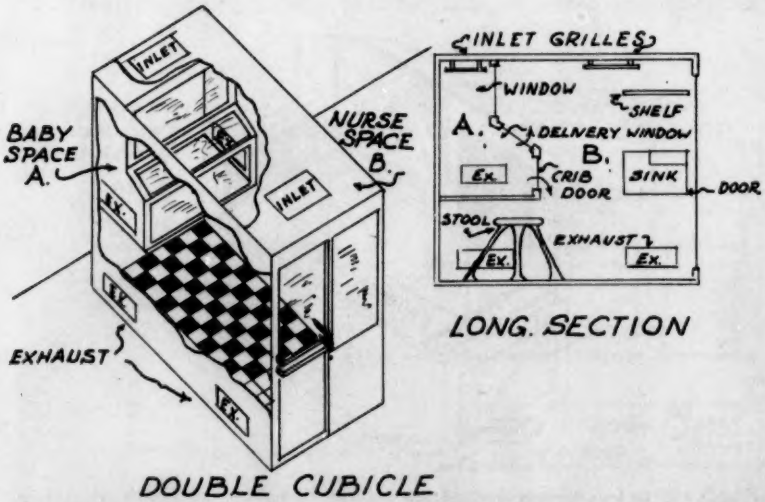

Fig. 4.—Double cubicle designed to allow nurse or attendant to work in a sitting position. Longitudinal section showing arrangement of inner cubicle and accessories.

tight and do not work loose. If the cubicle is bolted together, a gasket should seal the joints. Doors should be rigid and should swing against a soft rubber gasket. The floor should be sturdy and well braced and should be covered with a rubber flooring. The ceiling should be of single construction. Walls, ceiling and floor should be finished to allow the use of germicides and washes. We have specified uninsulated metal walls because of heat transmission, which permits the room in which the cubicles are located to be regulated for temperature and saves the cost of installing auxiliary heaters in the cubicles. It should be noted, however, that cubicles constructed of plywood and pressed wood have proved satisfactory.

The size of a double cubicle may vary but might well approximate the following: Baby space, 6 feet 4 inches by 3 feet by 2 feet; nurse

space, 6 feet 4 inches by 3 feet by 5 feet. When the delivery window is open the work area will be about 1 square foot, although this area may be increased. Cubicles are illuminated through the windows and by the use of auxiliary lights. These lights are located outside the cubicle so that they will not heat the interior. They shine through frosted glass windows located in the ceiling of the baby space and the nurse space. The switch for the light in the nurse space is located on the outside of the cubicle, and that for the light in the baby space is located in the nurse space.

Each nurse space contains a shelf above the sink or arm dip. If a sink is used, the services are carried on the outer wall of the cubicle. A hook for hanging the gown is located on a side wall. Other materials used in tending the baby may be placed on a cabinet which can be pushed out of the way under the baby cubicle. Each cubicle space is equipped with an electrical outlet, so that heating pads and other devices may be used.

VENTILATION

Ventilation of the cubicles will vary with the amount of money which can be spent on the ventilation system. My associates and I have constructed satisfactory cubicles in which no forced ventilation is used. We have, instead, increased the filter area and located filters in each cubicle space. The delivery window opening is protected with ultraviolet radiation. The most satisfactory type of ventilation, however, depends on a fan.

Cubicles may or may not be air conditioned. If they are, they may be controlled for temperature and humidity by locating the controls within each space, or by locating the controls for a battery of cubicles in the room. A satisfactory conditioning can be economically obtained by locating the cubicles in a room which is air conditioned from a central plant. The air into such a room should be filtered. The inlet for the cubicles is located in the room but is passed through filters located on each inlet of the cubicle. Air may be exhausted through the room system or out of the window. The cubicles are heated from the room. Humidity may be regulated for all cubicles by changing room conditions, or it may be regulated for the baby space by installing humidifiers. The same individual control may be obtained for temperature. In short, the control of temperature and humidity and the ventilation plan used will depend on the cost factor.

All cubicles, irrespective of the ventilation plan used, have inlet grilles located in the ceiling of each space and outlet grilles located near the floor. The inlet grilles should have a diffuser placed before them to prevent drafts, and the outlet grilles should be equipped with dampers so that ventilation differentials may be obtained in each space. Ducts supplying these grilles are carried on the outside of the cubicle.

Each inlet is equipped with filters, which may be of the glass wool or of the paper type. These may be changed without attendant's entering the cubicle. They are located in duplicate to prevent contamination in changing. Outlet ducts should also be equipped with filters, but these may be single.

If a central ventilation system cannot be used, the cubicles may be equipped with small fans of the centrifugal type, which run quietly and are inexpensive. These are located on the outside wall of the cubicle.

In order to prevent air currents from entering the baby space when the delivery window is opened, an air pressure differential may be maintained between the baby space and the nurse space so that the sweep of air is away from the baby. This air is then exhausted in the nurse space and does not reach the corridor. The same type of differential exists between the nurse space and the corridor, so that when one enters the nurse space the flow of air is to the corridor. This is a satisfactory method for preventing air-borne infective agents from reaching the baby. If low pressure differentials are preferred, additional protection may be obtained by the use of ultraviolet lamps.

The air in each chamber is frequently and thoroughly changed, and the cubicle is designed according to aerodynamic principles to prevent dead spots. An efficient clearing action prevents accumulation of bacteria in the air.

EXPERIMENTAL TESTING OF THE DOUBLE CUBICLE

Clinical studies on the usefulness and efficiency of the double cubicle system, together with proper bacteriologic controls, are being carried on at the Cradle, Evanston.[1] The tests that we have employed are of the engineering breakdown type.[2]

The efficiency of the system in preventing contact infection has been tested by placing cesarean-delivered (germ-free) animals in the baby space and tending them. Air-borne infection has been studied by spraying bacteria into the air from broth and saline solution to which mucus and dust are added. We have also used dry dust in the tests.

It must be emphasized that a system set up for control of normal conditions is one thing and one set up for breakdown tests is quite another. It is very doubtful if at any time the concentrations of micro-organisms used in these tests have been approached in the normal run of things. By the same token a germ-free animal is a far more sensitive indicator of contact infection than a normal animal or baby.

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2. Reyniers, J. A.: The Control of Cross Infection by the Use of Mechanical Barriers: I. Principles and Instrumentation for Absolute and Partial Control with Fixed and Circulating Hosts, in Cattell, J.: Biological Symposia, A. A. A., to be published; The Control of Cross Infection by the Use of Mechanical Barriers: II. Testing the Efficiency of Mechanical Systems for Controlling Cross Infection, ibid., to be published.

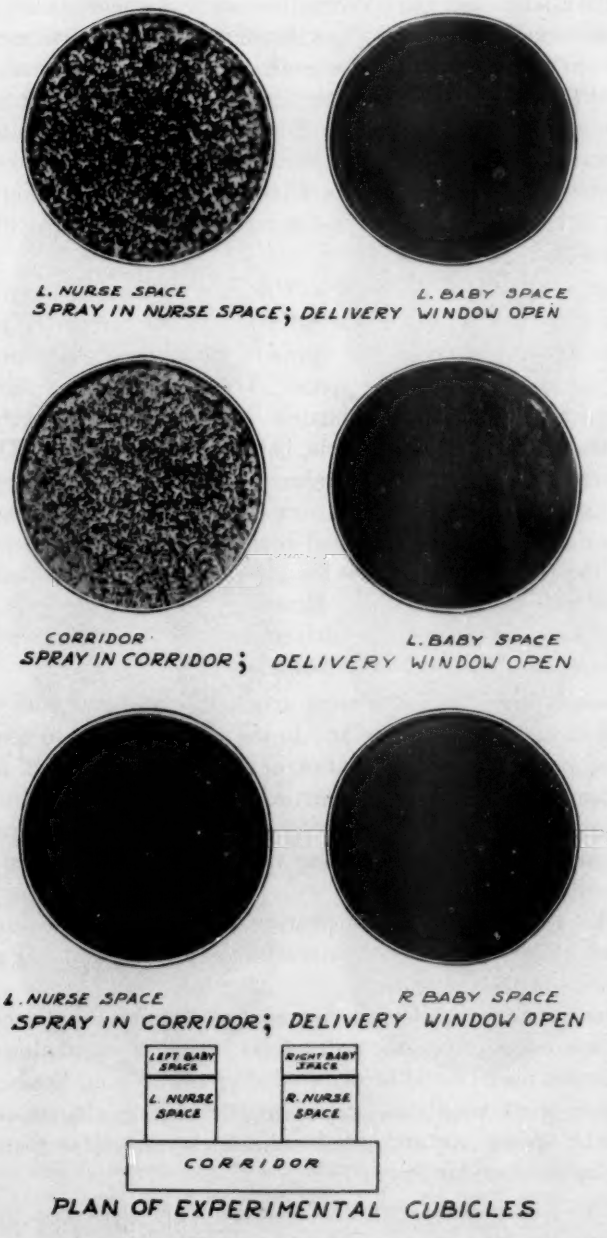

Fig. 5.—Contact photographs of a typical penetration experiment in which droplet nuclei formed from broth were used.

Glass Wool Filters.—These filters are of the commercial type charged with adhesive oil. When they were placed in tandem arrangement, neither droplet nuclei nor bacteria-charged dusts were carried through the filters when they were used to pass 600 cubic feet of air per minute. This is not true of single filters, which were about 90 per cent effective against the test sprays. Since the breakdown tests were many times more severe than normal conditions, it can be said that glass wool filters when used in tandem are effective protection in ventilating the cubicles either from a room in the manner specified or with 100 per cent outside air.

Penetration of Air Barrier.—The flow of air between the baby space and the nurse space was adjusted to 50 cubic feet per minute when the delivery window was opened. Organisms were sprayed from a broth culture into the nurse space. Test plates (fig. 5) show that the nurse space contained approximately 1,000 bacteria per cubic foot of air but that no penetration into the baby space took place. There was a slight penetration into the corridor, because the outer door was not sealed tightly. These results were substantiated by using titanium tetrachloride smoke and a Tyndal beam. When heavier droplets were used in the test and directed at the air barrier, penetration was effected at the aforementioned velocity. However, since the attendant is masked and only finer droplets can be driven through the mask, adequate protection was afforded at these velocities.

Clearing Action.—The clearing action has reference both to the distribution of air in the cubicle and to the time required to complete one change of air. An ideal distribution of air means a thorough penetration of the chamber by the incoming air, which should mix or dilute the stale air before being exhausted. Smoke is the best agent for studying the ventilation pattern and the clearing time. We used bacterial sprays in addition to the smoke.

Smoke studies indicated a clearing time of thirty seconds for the baby space, fifty seconds for the nurse space and four minutes and thirty-five seconds for the corridor.

Bacteria-charged vectors varied somewhat with the vector (droplet nuclei dust or mucus-formed droplets). When ventilation was shut down, droplet nuclei could be detected after twenty-four hours. All tests were made with ventilation calculated to be one change per minute in the baby space, two and a half minutes in the nurse space and five minutes in the corridor (fig. 6).

Aseptic Technics.—Germ-free animals were delivered by cesarean section into the baby space. Petri plates were exposed in the inlet and outlet ducts to check air-borne contamination. Mask, gown and glove technic was employed as a basic procedure. Contamination by Escherichia

coli or Sirratia marcascens could be set up in any vector line, for example in the sterilization of hands by the use of antiseptics. Another procedure employed was to handle normally born contaminated animals in an adjacent cubicle. Both double and single cubicles were tested. The length of time an animal remained free from contamination was

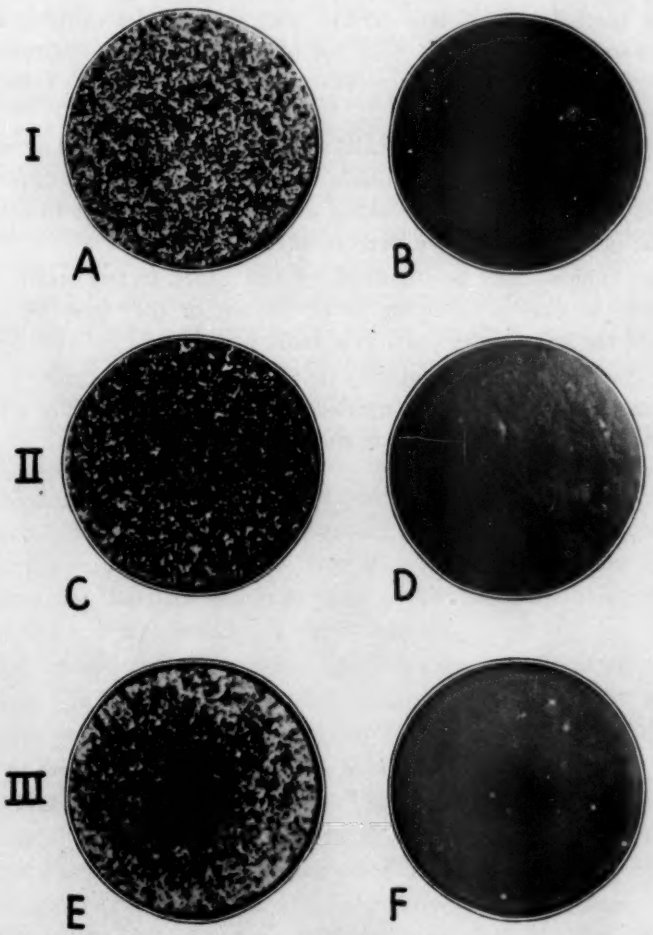

Fig. 6.—Contact photographs of a typical experiment to determine clearing action. *I*, clearing action of baby space, doors closed, spray in baby space: *A*, left baby space, fifteen minutes; *B*, left baby space, fifteen minutes. *II*, clearing action of nurse space, doors closed, spray in nurse space: *C*, left nurse space, immediate clearing; *D*, left nurse space, fifteen minutes. *III*, clearing action of corridor, doors closed, spray in corridor: *E*, corridor, immediate clearing; *F*, corridor fifteen minutes.

used as an index of the efficiency of the cubicle system. The detailed reports of these tests are the subject of another paper.[2a] At this time

and on the basis mentioned we are convinced of the greater efficiency of the double barrier system and its ease of use in rigid isolation. We have maintained animals germ free in this system for periods of over fourteen days.

SUMMARY

The double cubicle for the protection of babies against cross infection has been described, and certain tests used in determining its efficiency have been mentioned. The use of a double cubicle is theoretically better than the use of a single cubicle, and engineering tests substantiate the theory.

Such cubicles may be produced at a very low cost, and when once set up are inexpensive to maintain, besides offering the advantage of being constant in effect and making aseptic technics easier to carry out by virtue of mechanizing the steps involved.

These cubicles may be standardized and added to any room, so that there need be only a minimum of alteration; or they may be planned as part of the construction of a new building.

The double cubicle system may be elaborated for maternity hospitals by making a room into a double cubicle through the addition of a barrier, thus making it possible to isolate mother and baby.

RETINOBLASTOMA OF INFANTS AND CHILDREN

ITS SIGNIFICANCE AS A PEDIATRIC PROBLEM

SAMUEL J. NICHAMIN, M.D.

DETROIT

A malignant tumor of the retina which occurs almost exclusively in infants and in young children would seem to be of primary concern to the pediatrician. Although malignant tumors in general are relatively infrequent in children, from the standpoint of mortality their significance is disproportionately great in comparison with other childhood diseases. About two thirds of the retinoblastomas which have been the subjects of the numerous reports in the world literature for more than a hundred and fifty years have been in children under 4 years of age. The appearance of such a highly malignant neoplasm in this early age period is a frightful catastrophe both to the patient and to the family. The full-blown clinical picture in the later stages of the growth's development is replete with tragic and horrible manifestations. This is a tumor the efficacy of treatment for which is dependent for the most part on early diagnosis. An awareness of the possibility of a malignant tumor of the immature eye, in addition to a familiarity with its incipient objective symptoms, on the part of the average pediatrician would undoubtedly prevent delay in diagnosis of this dread disease.

Scant consideration has been given to this condition in pediatric literature. In fact, there is no reference to it in two recent foremost American pediatric textbooks. Apart from consideration of this condition as one of a group of tumors in a paper by Martin [1] on "Cancer of the Head and Neck in Children" in a symposium on "Tumors in Childhood," I have been unable to find any paper strictly devoted to the subject during the past twenty-five years in the chief pediatric journals.

Fortunately, retinoblastoma is a relatively rare disease, forming according to Berrisford [2] about 0.01 per cent of all the diseases of the eye. Hemmes [3] reported the results of a survey in the Netherlands showing that retinoblastoma occurs once in 34,000 living children born in

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From the Children's Hospital of Michigan and the Department of Pediatrics, Wayne University Medical School.

1. Martin, H. E.: J. Pediat. **15**:363-371 (Sept.) 1939.
2. Berrisford, P. D.: Roy. London Ophth. Hosp. Rep. **20**:296, 1916.
3. Hemmes, G. D.: Klin. Monatsbl. f. Augenh. **86**:331, 1931.

that country. It certainly cannot be considered a major pediatric problem. There is little opportunity for clinical observation and study of this cancer of infants and children in most pediatric centers. Further diffusion of data would therefore be indicated through the customary channels of the literature on diseases of infancy and childhood.

Ever since Virchow [4] named this disease glioma of the retina there has been a great deal of confusion in its terminology. The multitude of names used in an effort to find a rational explanation of this retinal tumor mirrors a lack of unanimity of opinion as to its exact nature. Prior to the development in the knowledge of histopathology it had often been reported as cancer of the eyeball, fungus hematoides and amaurotic cat's eye. Other terms that have been used to designate it are retinoma, neuroma, neuroma ganglionare, neurocytoma, neuroepithelioma, neuroglioma, neuroblastoma, medullary neuroma, gliosarcoma and neurocellular sarcoma of the retina. However, Virchow's term, glioma of the retina, has persisted and has been more universally employed than its officially accepted name of retinoblastoma. Martin [1] in the aforementioned recent paper still referred to the condition as glioma of the retina. Jackson [5] pointed out that the use of this term prevents a clear understanding of the disease, causing confusion with glioma of the brain. Hu [6] differentiated the neoplasm from glioma of the brain by its rapid growth, greater tendency toward metastasis and lack of glia fibers demonstrable by ordinary staining methods. In other words, the older term, glioma of the retina, is erroneous. The cells are not glia cells, and the growth is completely different from that of glioma of the brain.

The term retinoblastoma was chosen by Verhoeff and officially accepted by the American Ophthalmological Society in 1926. It accurately identifies the tumor as arising from retinal germ cells, i. e. cells set apart for the development of the retina. This tumor arises from the posterior part of the retina and consists of small, closely packed round or polygonal cells with large, darkly staining nuclei and scanty cytoplasm —an appearance similar to that of partially differentiated cells of the fetal retina. Special stains show the delicate processes of the cells. They often present a radial arrangement in tubules of about ten to twenty cells in thickness around blood vessels. Rosettes which are sometimes seen are believed to be derivatives of the early rods and cones. Cells farthest away from the blood vessels die from lack of nutrition, giving rise to frequent degenerative changes. Accordingly, the tumor grossly appears

4. Virchow, R.: Die krankhaften Geschwülste, Berlin, A. Hirschwald, 1864, vol. 2, p. 123.

5. Jackson, E.: Retinoblastoma and Recent Views of Malignancy, J. A. M. A. **87**:1471-1477 (Oct. 30) 1926.

6. Hu, C. H.: Am. J. Path. **6**:27-38 (Jan.) 1930.

crumbly and friable. In color it is gray or milky white, soft and usually interspersed with gelatinous areas of degeneration, patches of calcification and pigmented hemorrhages. Most of the usual histologic features of retinoblastoma may be noted in the photomicrograph, which represents a section of the tumor mass of the enucleated eye of J. C., the case record of whom appears in this article.

Histologic section of retinoblastoma showing a characteristic picture, with areas of necrosis, tubules of cells arranged radially around blood vessels and a tendency toward rosette formation.

In the early stages of growth of the neoplasm, several varieties may be distinguished on the basis of location and direction of growth. Two of these have been characterized as exophytum and endophytum. In the former type several pinhead-sized nodes appear on the retina and spread in the subretinal space, later forming a tuberous deposit on the outer surface of the detached retina. Early, this condition simulates a simple

detachment of the retina, which in young children must be regarded as a suspicious finding. The endophytum type grows primarily toward the vitreous. The retina remains attached to the choroid. The mass first appears in the form of a small round yellowish-white nodule, which soon becomes surrounded by small satellites. It then spreads on the inner surface of the retina, to which it is intimately united by processes. Later polypoid masses grow into the vitreous surface. In contrast to intraocular sarcoma, there is no pigmentation in retinoblastoma.

More examples have been noted in the white race than in the Negro. Sex does not appear to be an important factor. The tumor has been found bilaterally in 20 to 30 per cent of cases. Most observers believe that the growth in the second eye arises from an independent focus. Although both eyes may be involved at birth, it is more usual for the neoplasm to be noticed in the second eye several months, or even years, after it appears in the first.

That hereditary factors may play a more or less significant role in the incidence of retinoblastoma is manifested by the evidence of its multiple occurrence in certain families, as culled from a number of reports in the literature. In view of the aforementioned extreme rarity of the condition, its predominant occurrence in certain families is of more than chance significance and argues for consideration of a familial type of retinoblastoma. In a discussion of the inheritance of retinoblastoma and its relationship to practical eugenics, Weller [7] postulated the existence of two separate disease entities: familial retinoblastoma and sporadic retinoblastoma. While reporting an additional case of the familial type, he pointed out that there have already been more than 25 reports of this type of retinoblastoma in the literature. However, it should be stressed that the sporadic type is far more frequent than the familial. The indications for the application of eugenic measures would therefore be rather vague. On the other hand, with a disease so very tragic in its effects the need for eugenic prophylaxis should not be completely ignored. With more complete and intensive genetic studies, in Weller's opinion, a relationship between the sporadic and the familial type may become established. Some data in this direction have been presented by Lange.[8] From the standpoint of racial improvement and prevention of the disease Weller expressed the opinion that it would be justifiable to recommend sterilization of any child surviving retinoblastoma and to advise parents of a child with the disease against having further children.

The clinical course of retinoblastoma is divided into four stages, based on its natural history and development. The first is the stage of intraocular growth. The eye gradually becomes blind, and the growth may be

7. Weller, C. V.: Tr. A. Am. Physicians **55**:308-312, 1940.
8. Lange, H.: Klin. Monatsbl. f. Augenh. **101**:854, 1938.

seen either with the naked eye or with an ophthalmoscope. The second is the stage of secondary glaucoma. The eyeball becomes harder, congested and painful. The cornea may become clouded or edematous. Various types of ectasia may develop in the cornea or sclera. The third is the stage of extraocular extension, either by way of the optic nerve or by the vessels or nerves which perforate the sclera. The fourth is the stage of metastasis to distant parts of the body.

The first, or intraocular, stage, before acute symptoms develop, usually lasts from six months to a year. There is a fairly typical clinical picture presented by most of these neoplasms. Ordinarily the growth remains silent and unnoticed until it has developed sufficiently to produce the first symptom, which is in the nature of a peculiar yellow reflex at the pupil, resembling a cat's eye shining in the dark. The condition has consequently been called "amaurotic cat's eye" by some of the older writers. In some cases the parents may notice that the child is unable to see with the affected eye. In this first stage, pain or redness of the eye is not present. The media are clear. There may be slight dilatation of the pupil. The child's health appears normal. The earliest aspects of the growth of the tumor are not often seen, except when after known involvement of one eye the second is kept under constant observation. The tumor then appears ophthalmoscopically in one or another form as described. As the retinoblastoma grows progressively larger it finally fills the eyeball completely.

The second stage of increased tension varies in duration within wide margins, with a possible average of about seven months. During this period the child may become irritable and emaciated. There may develop an enlargement of the globe, with stretching of its coats. This process is associated with a great deal of pain. Changes in the size and appearance of the cornea develop, and finally the sclera may be perforated, with consequent relief of pain.

As soon as perforation of the eyeball by the tumor has occurred, there is an increased impetus in its growth, which is then relieved of the confining intraocular pressure. The orbit becomes filled. Its bony walls may be invaded by the tumor cells. Proptosis develops, and the tumor forms a large fungating, ulcerating mass which bleeds easily and bulges forward between the lids, forming a rather horrible picture. From the appearance of the tumor mass in this terminal stage, the condition became known as fungus hematoides oculi in the older literature. In spreading out of the eyeball, the tumor usually extends along the optic nerve to the base of the brain, frequently in the region of the optic chiasm. This type of spread by direct extension is in the nature of a slow, progressive permeation. Death may result from increased intracranial pressure. The tumor cells that infiltrate the optic nerve present a threadlike and

branching appearance interspersed among the nerve fibers and connective tissue septums, in contrast to their round contour inside of the eyeball. These cells are looked for when sections of the optic nerve are examined to determine whether the tumor has spread back from the eyeball. Another method of direct extension is through the sclera into the orbit along the perforating vessels. Visceral metastases from retinoblastoma are rarely seen, since extension occurs first along the optic nerve, producing cerebral involvement, which in turn causes death relatively early.

The differential diagnosis chiefly involves a differentiation between a neoplastic and a non-neoplastic mass situated behind the lens. There are a number of ocular conditions occurring in children which produce a white mass in the vitreous and might thereby be mistaken for a malignant neoplasm. This is especially true of an organizing mass of exudate resulting from metastatic ophthalmia, associated at times with epidemic meningitis and rarely with scarlet fever and measles. Syphilitic gumma, large caseating choroid tubercle, retinal or subretinal hemorrhage with detachment of the retina, and persistent posterior fibrovascular sheath of the lens may be among other conditions simulating neoplasm. The history of the case, the characteristic appearance of the tumor mass and the intraocular tension are all factors that are of help to the ophthalmologist in reaching a probable diagnosis of retinoblastoma.

The treatment of retinoblastoma consists essentially of enucleation of the tumorous eye at the earliest possible moment. If no extraocular extension has occurred by this time, one can safely assure the parents of a favorable prognosis as to life. With the enucleation of the eyeball it is essential that the largest possible portion of the optic nerve be removed. Serial sections of the severed end of the nerve should be made immediately in paraffin and examined histologically. If no tumor cells can be found, there is nothing further to be done. It must be noted, however, that a discontinuous spread may sometimes be found past a healthy segment. In general, one can state that the presence or absence of infiltration in the optic nerve may serve as a decisive factor in the evaluation of prognosis. In an extensive series of cases, Reese [9] found that in cases without apparent extraocular extension the favorable prognosis after excision is 57 per cent. This has been confirmed by other investigators. When orbital extension has occurred, one may have to resort to exenteration of the orbit or heavy irradiation. The latter type of treatment is often applicable in cases of bilateral retinoblastoma. After enucleation it is essential to watch carefully for any local recurrences in the socket, which may appear within four months but seldom develops after a year. Postoperatively, a course of high voltage roentgen treat-

9. Reese, A. B.: Extension of Glioma (Retinoblastoma into Optic Nerve), Arch. Ophth. 5:269-271 (Feb.) 1931.

ments over a period of several months may be employed routinely as an extra precautionary measure in a prognostically favorable case.

A fairly accurate estimation of the prognosis in cases of retinoblastoma may be made by noting the stage in which the growth has been removed. Prognosis as to life is excellent if the enucleation of the eye was carried out in the first stage, before symptoms of secondary glaucoma appeared. Patients with no gross extrabulbar extension in whom enucleation was performed in the second, or glaucomatous, stage have about a 50 per cent chance of survival. However, death is practically certain in all cases in which enucleation is done after extraocular extension of the tumor.

REPORT OF A CASE

On Sunday, April 6, 1941, the mother of the patient, J. C., telephoned requesting advice for treatment of her child's right eye, which, she stated, had appeared "blood-shot" for a few days. Further questioning elicited the fact that on the preceding Tuesday the patient while playing had fallen and struck her forehead violently against the foot of the bed. There had been no loss of consciousness and no apparent bruising. Nausea, vomiting or dizziness had not been noted. Since that incident the mother added that the child had appeared lethargic, had suffered from fatigability and drowsiness and had complained of headache around her right eye and in the right side of the forehead. The mother was not definitely aware of any gross disturbance of vision. Irritability and loss of appetite were additional complaints. Hospitalization was advised.

Past History.—The girl was born March 11, 1938. The delivery was normal. Her weight at birth was 5 pounds 2 ounces (2,324.7 Gm.), and her condition at birth was normal. No congenital abnormalities were noted. There was a normal feeding and developmental history. The first tooth appeared at 6 months. She sat up at 6 months, walked at 1 year and talked at 1½ years. She had received all the usual immunizations.

On Nov. 7, 1939, at the age of 19 months, the child was hospitalized because of convulsions associated with an infection of the upper respiratory tract and bilateral otitis media. There had been no other serious illnesses.

Family History.—The mother, 30 years old, was living and well. The father, 32 years old, was likewise in good health. There had been no other pregnancies. No relevant information was obtainable as to any familial history of congenital abnormalities of the eyes.

Physical Examination.—The child's temperature at the time of the examination was 99.8 F. Her height was 38 inches (96.5 cm.) and her weight 34 pounds (15.4 Kg.). She was a well developed and well nourished 3 year old girl, rather irritable, restless and uncooperative. The skin was clear. The head was of normal contour. There were no apparent bruises, lacerations or hematomas. No areas of tenderness could be palpated. There was slight injection of the right eye. The right pupil appeared moderately dilated as compared with the left. There was a slight reaction to light. The iris appeared dull and discolored. Extraocular movements were normal. The pharynx, tonsils, tongue and teeth were normal. A few small cervical glands were palpated. There was no rigidity of the neck. The heart and lungs were normal; the liver and spleen were not enlarged; the abdomen was soft, and no masses were discerned. The extremities

and all the deep and superficial tendon reflexes were normal. There were no abnormal neurologic findings.

Laboratory Examinations.—Roentgen examination of the skull showed no evidence of fracture, of increased intracranial pressure or of abnormal calcification. The hemoglobin content was 14.1 Gm. per hundred cubic centimeters; the white blood cell count, 11,900 per cubic millimeter. The Kline reaction of the blood was negative. The urine was normal.

Ophthalmologic Consultation (Dr. Howell L. Begle).—The report read as follows: "The right eye is slightly red, but the conjunctiva and lids are not abnormal. The tension of the right eye is definitely (with fingers) higher than that of the left. There is no proptosis. Movements are apparently normal. A homatropine disk was placed in the sac and the eye examined one-half hour later. The pupil showed a yellowish green reflex from the vitreous. With the ophthalmoscope, +20, a greenish yellow mass occupying the lower part of the vitreous was seen. A red reflex with no actual details was seen in the upper part of the fundus. The iris was discolored, but there were no adhesions. The pupils were round."

The impression was that of an intraocular tumor mass or exudate. A tentative diagnosis of retinoblastoma was made. Further confirmation of this diagnosis was obtained after consultations with Dr. Walter R. Parker and Dr. Harry Gradle, both of whom likewise advised immediate enucleation of the involved eye.

Course.—On April 12, 1941, the right eye was enucleated by Dr. Walter R. Parker. The optic nerve was severed several millimeters beyond the eyeball. Externally the eyeball had a normal appearance. There was no evidence of any gross perforation of the eyeball by the tumor mass. Postoperatively, the patient was given a series of three high voltage roentgen treatments at intervals of six weeks. Thus far, careful follow-up examinations have revealed no evidence of local recurrence of the malignant growth.

Microscopic Examination (Dr. Parker Heath).—The report was as follows: "Section of a juvenile, incomplete eye, anterior segment, and some cross sections of the optic nerve: The section shows a thickened cornea and a shallow infiltration angle. The ciliary processes are partially covered by debris and some exudate. The vitreous is a large mass of hemorrhage and cells. The latter in some areas have a peritheliomatous arrangement about the blood vessels, suggesting rosettes in form. There are numerous mitotic figures in cells, and some necrosis from lack of blood supply. The cross sections through the nerve fail to show any malignant cells infiltrating this tissue. Diagnosis: retinoblastoma."

COMMENT

Recognition of the early symptoms and signs leading to early diagnosis is the sine qua non of control of cancer. With certain forms of malignant growth in the adult, early diagnosis and cure can be obtained when characteristic objective symptoms or signs are prominent in the initial stages. Such symptoms as pain and dysfunction of an organ are rarely evident during the early growth of retinoblastoma in the young. In the case that I am reporting, pain appeared to be a relatively minor complaint and was mentioned only after detailed questioning of the patient's mother. Likewise, disturbance of vision remained unnoticed,

although it must have been present probably for a period of several months. The first symptom that prompted the mother to seek medical advice was the purely objective symptom of a reddened eye. The additional history of a violent fall suffered by the patient prior to the onset of symptoms proved to be irrelevant, except as a possible revelation of defective vision. The possibility of intracranial injury was ruled out at the outset, after a thorough neurologic examination and negative roentgenologic findings. The presence of a dilated pupil, incipient increase in intraocular tension and changes in the cornea and iris appeared to restrict the pathologic process to the eyeball. With these symptoms interpreted with reference to a tumor within the eyeball, one could estimate that the neoplasm had already passed the first stage, of intraocular growth, and had progressed to the initial period of the second stage, of secondary glaucoma. That the tumor had reached this stage of development was substantiated after enucleation of the eye, when it was noted that the neoplasm almost filled the globe with no visible perforation and no extraocular extension. Furthermore, microscopic examination of the severed end of the optic nerve did not reveal any infiltration with tumor cells.

Most cases reveal a similar history and course. It is therefore apparent that in making a diagnosis of retinoblastoma in an infant or young child one must rely principally on objective signs. In spite of the presence of certain telltale or suspicious objective ocular symptoms, it has been estimated that there is an average delay of about four months between such early manifestations and the making of the correct diagnosis. If the pediatrician would bear in mind the possibility of a malignant tumor of the eye in a given case, such a delay in diagnosis would seldom occur. An important early symptom is dilatation of the pupil. In later stages a white reflex may be seen through the pupil. A persistent inequality in the size of the pupils should not be disregarded. Any patient with such an anomaly deserves a thorough investigation by an ophthalmologist to rule out the possibility of retinoblastoma.

SUMMARY

A case of retinoblastoma in a 3 year old child is reported. This is a malignant retinal neoplasm of infancy and childhood which is curable if an early diagnosis can be made. Hitherto this cancer, which occurs almost exclusively in the young, has been given due consideration almost solely in the ophthalmologic literature. Familiarity with its earliest objective manifestations is the responsibility of the pediatrician. A discussion relating to its nomenclature, pathology, symptomatology, diagnosis and treatment is presented.

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Abstracts from Current Literature

Biochemistry; Bacteriology and Pathology

A Change in the Bacteriologic Technic When Sulfapyridine Is Administered to the Patient. G. Korthof, Nederl. tijdschr. v. geneesk. **84**:2793 (July 27) 1940.

From bacteriologic examination of blood and cerebrospinal fluid of patients treated with sulfanilamide preparations, it was found that these fluids, which under normal conditions and with a suitable technic can be excellent culture mediums, acquire a bactericidal action within a few hours after the patients ingest these drugs. This was demonstrated for hemolytic streptococci, Streptococcus viridans, pneumococci and meningococci. Blood or cerebrospinal fluid for bacteriologic examination should therefore be taken before the intravenous injection, and in case of intramuscular, subcutaneous or oral administration no later than immediately after the administration of the sulfanilamide compounds.

van Creveld, Amsterdam, Netherlands.

Vitamins; Avitaminoses

Distribution of Ascorbic Acid in the Blood and Its Nutritional Significance. Allan M. Butler and M. Cushman, J. Clin. Investigation **19**:459 (May) 1940.

Evidence is presented that the apparent ascorbic acid concentration of the white blood cells plus platelets of patients not suffering from infection or leukemia is a better index of physiologically significant deficiency than the plasma concentration.

The occurrence of very high concentrations of an ascorbic-acid-like reducing substance in the buffy coat of centrifuged leukemic blood was confirmed.

Guest, Cincinnati.

The Mechanism of the Excretion of Vitamin C by the Human Kidney at Low and Normal Plasma Levels of Ascorbic Acid. Gerald J. Friedman, Sol Sherry and Elaine P. Ralli, J. Clin. Investigation **19**:685 (Sept.) 1940.

Sixty-nine observations of the clearance of vitamin C at plasma levels varying from 0.03 to 2.05 mg. per hundred cubic centimeters suggest that the reabsorption of the vitamin is never complete and that the clearance of vitamin C at the low plasma levels is constant and independent of the plasma concentration.

Authors' Summary.

Vitamin C Requirements of Native Mine Labourers. An Experimental Study. F. W. Fox, L. F. Dangerfield, S. F. Fottlich and E. Jokl, Brit. M. J. **2**:143 (Aug. 3) 1940.

"Two groups, each of 950 mine laborers, chosen so as to be as comparable as possible in respect to tribe, age, physical condition and occupation, were subjected to an experimental test. One group remained on the usual mine diet, which was estimated to contain from about 12 to 25 mg. of ascorbic acid, while to the other an additional daily ration of 40 mg. of ascorbic acid was administered in the form of a standardized orange-juice concentrate. The experiment was continued for seven months, and the behaviour of the two groups was studied in various ways Both groups maintained a high level of general health.

"Twelve cases of scurvy occurred in the untreated group and one mild case in the group receiving the additional ration of ascorbic acid. Otherwise no significant difference could be detected in the behaviour of the two groups. Thus the weight changes were almost identical, and there was no evidence that the general health, physical efficiency, and resistance to infectious or dental diseases had been increased. The additional ration of vitamin C was discontinued as soon as a patient reached hospital, but there was no indication that the change in the previous diet had improved the rate of recovery from disease, or that the rate of healing of wounds and fractures had been accelerated. Nearly three-quarters of the individuals examined by the dental surgeon in both groups were found to possess healthy gums.

"Numerous tests showed that the plasma ascorbic acid values were extremely low, even in apparently healthy individuals engaged in hard work. These low values were not significantly raised by the additional daily ration of ascorbic acid.

"Conclusions:

"1. Taken as a whole the evidence presented in this study shows that the native mine labourer possesses considerable powers of adjustment to a diet low in antiscorbutic vitamin—in fact, his daily requirement, even when engaged in strenuous physical exercise, seems to be very small indeed.

"2. A net daily intake of about 15 mg. of ascorbic acid, perhaps even less, can evidently protect the majority of such individuals from scurvy. An addition of ascorbic acid did not diminish the incidence of infectious diseases, nor did it improve dental health or physical efficiency. Alternatively, scurvy was not found to occur more frequently or more quickly amongst mine labourers engaged in the more strenuous occupations.

"3. The precarious nature of such minimal rations in respect to the production of scurvy was also well illustrated by this experiment, since a number of cases occurred in the untreated group, whilst the disease was virtually abolished in those receiving the additional protection.

"4. Attention was drawn to the singular lack of correlation obtained between the various tests available for detecting vitamin C deficiency and the clinical findings. While these tests may be useful in so far as they draw attention to the existence of low reserves of the vitamin, in our hands they failed entirely to distinguish those individuals who were any the worse for such low reserves.

"It is made clear that the object in drawing attention to these observations is not to minimize the importance of this vitamin in human nutrition or to advocate the use of diets that are only just capable of protecting the consumer against scurvy but much still remains to be learnt about the part played by ascorbic acid in the general metabolism and the claims advanced cannot as yet be regarded as fully established. In the meantime the assertions so confidently made by uncritical observers should be accepted with considerable reserve."

ROYSTER, University, Va.

VITAMIN C IN THE INFANT. JAVIER R. MENDILAHARGU and E. L. ZAVALA RODRIGUEZ, An. Soc. puericult. Buenos Aires **6**:109 (April-June) 1940.

The studies reported were repeated several times, and one of the observations follows:

The study was made on 4 infants aged from 2 to 9 months, 2 from 10 to 11 months and 4 from 14 to 30 months. All were healthy and had been proved before the experiment to have a concentration of ascorbic acid in the urine of about 2 mg. per hundred cubic centimeters (which showed that the organism was saturated). These infants were placed on a diet with no vitamin C, and the urine was examined every twenty-four hours.

The infants of 2 to 9 months had good urinary elimination of vitamin C (interpreted as a permanent saturation of the organism).

One of the infants of 10 to 11 months had ascorbic acid in the urine, and the other did not. In the case of the infants of 14 to 30 months, from forty-eight hours on there was no vitamin C in the urine.

The diet consisted of 1 liter of a gruel containing 5 per cent oatmeal, 5 per cent sugar, 14 grains (0.9 Gm.) of casein and 4 grains (0.025 Gm.) of brewers' yeast.

The authors draw the following conclusions: 1. Breast-fed babies always have a quantity of vitamin C to cover their needs; infants fed cows' milk do not. 2. The power of synthesis of vitamin C is lost at the age of 12 months.

GIFFEN, Toledo, Ohio.

VITAMIN C CONTENT IN PREGNANCY. H. BRIEGER, Ztschr. f. Geburtsh. u. Gynäk. **121**:80, 1940.

Previously described evidence of lack of adequate vitamin C in pregnancy is corroborated. In guinea pigs, dogs and rats (only in the kidneys) this lack is in part compensated for by autosynthesis in the visceral organs of the mother and toward the end of the pregnancy in the placenta. The organs of the fetus synthesize little if any vitamin C. When the level of vitamin C intake falls, a compensatory mechanism increases the production of the vitamin in these animals.

ADAIR, Chicago.

CAN SKIM MILK BE MADE ANTIRACHITIC BY IRRADIATION? K. SCHEER, Ztschr. f. Kinderh. **62**:104 (Aug. 9) 1940.

After irradiation of skim milk, the cream was replaced and the milk was fed to an 18 month old boy with florid rickets. After fourteen months the rickets was practically healed. For comparison, another child, 2 years old, with florid rickets was given irradiated whole milk, with almost complete healing in nine weeks. The antirachitic factor in skim milk is presumably a stearin combined with proteins, especially lactalbumin.

SIEMSEN, Chicago.

HIP BERRIES AS A SOURCE OF VITAMIN C. B. HAMMAR and J. SCHRÖDERHEIM, Svenska läk.-tidning. **37**:953 (May 31) 1940.

The vitamin C content of fresh hip berries is variable, depending on the sort of hip tree and on the degree of ripeness. Some kinds of hip berries do not contain any appreciable amount of the vitamin. The average value is 0.5 to 0.6 per cent. In dried berries the content also varies in considerable degree, depending on the mode of drying; usually it is only 0.1 to 0.7 per cent but it may reach 1 to 1.6 per cent. In dried powdered hip berries the vitamin C content is low, from 0.04 to 0.42 per cent. During one year's preservation the content decreases about 50 per cent in powdered, but only insignificantly in ordinary dried, hip berries. A soup of hip berries is best prepared in the following way: The crushed berries are quickly stirred into the boiling water, and a tightly closing cover is put on the vessel. After ten minutes the soup is strained and the rest is washed with boiling water. The strained and washed fluids are mixed, thickened and boiled. A hip berry tea is prepared by mixing one part of crushed dried hip berries and ten parts of boiling water, and boiling for five to fifteen minutes. After cooling the fluid is strained and the rest of the berries are pressed and washed. Such a tea may contain 40 mg. of ascorbic acid in 100 cc. and can be kept for a few days without appreciable loss of the vitamin.

WALLGREN, Göteborg, Sweden.

DETERMINATION OF VITAMIN C CONTENT IN BLOOD AND URINE OF PATIENTS WITH DISEASES OF SKIN AND WITH VENEREAL DISEASES. R. KOOY, Nederl. tijdschr. v. geneesk. **84**:1394 (April 13) 1940.

Determination of the vitamin C content in the blood and urine of 53 patients with cutaneous and with venereal diseases showed that patients with erythroderma

and erythrodermic exanthema had very high saturation values. Certain diseases, such as eczema, psoriasis vulgaris and syphilis, are not characterized by definite saturation values; there the vitamin C content probably depends on the extension and intensity of the malady. The author doubts the therapeutic value of vitamin C for conditions such as psoriasis vulgaris and erythroderma. Daïnow's opinion (1937) that determinations of vitamin C in patients treated with neoarsphenamine are unreliable is not of general significance, but the value found is dependent on the method used. The author was unable to confirm the hypothesis of Daïnow that there is a relation between the tolerance for neoarsphenamine and the saturation with vitamin C.

VAN CREVELD, Amsterdam, Netherlands.

INFLUENCE OF THE NATURAL CONTENT OF RADIUM EMANATION OF THE ATMOSPHERE ON THE DEVELOPMENT OF RICKETS. M. J. L. DOLS and B. C. P. JANSEN, Nederl. tijdschr. v. geneesk. **84**:3050 (Aug. 10) 1940.

It is a well known fact that the liability to rickets even when the experimental subjects are kept in the dark is not at all constant throughout the year. Dr. Dey, in the laboratory of Professor Clay, at Amsterdam, had found that the radon content (amount of radium emanation) of the atmosphere is also very fluctuant during the year. Further, Dr. Dey had seen that the radon content 10 meters above the surface of the earth is less than half that at the surface. So the authors kept one batch of young rats in a room in the cellar and another batch of rats, litter mates, on the same rachitogenic diet in a room 10 meters higher. Both rooms were darkened. The rats in the upper story got severe rickets, and the rats in the cellar did not get rickets at all. The authors think that the radon content of the atmosphere has a distinct influence on the prophylaxis of rickets.

VAN CREVELD, Amsterdam, Netherlands.

Newborn

ACTION OF MENADIONE (FORM OF VITAMIN K) ON PROTHROMBINEMIA OF THE NEWBORN. F. CISLAGHI, Med. ital. **21**:181 (May) 1940.

The author determined the index of prothrombinemia in the blood of 20 newborn infants, using a modification of the method of Quick. He concludes that vitamin K activates the formation of prothrombin and that administration of menadione (2-methyl-1, 4-naphthoquinone) is advisable in cases of hemorrhagic tendency in the newborn.

MARTOCCIO, Utica, N. Y.

HEMORRHAGIC DIATHESIS IN THE NEWBORN AND ITS TREATMENT WITH BLOOD TRANSFUSIONS. P. N. DAMM, Ugesk. f. læger **102**:620 (June 13) 1940.

An account is given of the causes of hemorrhagic diathesis in newborn infants. The author is of the opinion that in many cases it probably is due to K hypovitaminosis. The best treatment is considered to be transfusion of blood into the longitudinal sinus. He reports on 19 patients treated in various ways, 2 of them by blood transfusion. Three of the children died.

WALLGREN, Göteborg, Sweden.

TWO CASES OF ICTERUS GRAVIS NEONATORUM. J. DRUKKER, Nederl. tijdschr. v. geneesk. **84**:3053 (Aug. 10) 1940.

After an introduction in which the important characteristics of icterus gravis are discussed, the author reports 2 cases of the disease observed in brothers. The disease in both cases had a protracted and intermittent course; in one case the jaundice reappeared and in the other one the erythroblastemia suddenly reoccurred. In the author's experience an abnormal prolongation of the prothrombin time cannot be regarded as a new symptom of icterus gravis neonatorum. Yet administration of vitamin K may be useful in this disease. The preferable treatment

must be blood transfusion, as early as possible. It may also be of some importance to give a cholagogue. As far as etiology is concerned, the suggestion is given that a constant factor is present in fetal erythroblastosis which, depending on the sensitivity of the organism, in the different periods of early life gives rise to either congenital hydrops or icterus gravis or anemia of the newborn.

VAN CREVELD, Amsterdam, Netherlands.

A CASE OF MECONIUM PERITONITIS. J. F. O. HUESE, Nederl. tijdschr. v. geneesk. **84**:3083 (Aug. 10) 1940.

The author describes meconium peritonitis in a newborn infant, who at birth already had an enormous abdomen. Surgical intervention was resorted to, as a congenital occlusion was thought to exist, but two perforations of the small intestine were found. The child died. VAN CREVELD, Amsterdam, Netherlands.

Acute Contagious Diseases

THE USE OF DIPHTHERIA ANTITOXIN AND TOXOID IN LEPROSY: A PRELIMINARY REPORT. D. R. COLLIER and J. HUGH MCKEAN, Leprosy Rev. **11**:140 (July) 1940.

Oberdoerffer advanced the theory that adrenal insufficiency, sometimes caused by the presence of sapotoxin in certain foods, predisposes persons to leprosy. It is well known that the body forms antibodies against diphtheria toxin, which essentially damages the adrenals, and does not tend to form such antibodies against leprosy. It might be possible that diphtheria antitoxin would neutralize leprosy toxin elaborated during the stage of leprous reaction.

A number of patients who were having repeated leprous reactions were given diphtheria antitoxin during the acute stage. After an initial intensification of symptoms, clinical improvement occurred. The reaction subsided; the leprous nodules flattened; the elevated red areas became brown, and the overlying skin became scaly and crinkly. Microscopic examination showed fragmentation and granulation of the bacilli. All these signs are usually associated with acquisition of natural resistance to leprosy and signify that the infection is past its peak. No such changes were induced in control cases, in which tetanus antitoxin or antivenom was administered in place of diphtheria toxin.

Since these results were so encouraging, it was decided to try diphtheria toxoid. Improvement started within two weeks and manifested itself by change in pigmentation from red to brown and a wrinkling effect of the skin, indicating shrinking of the nodules and flattening of the plaques. Granulation and fragmentation of bacteria occurred. Some patients experienced paresthesia of areas formerly anesthetic; some had complete return of sensation, and 1 had return of function of a partly paralyzed hand. More than 50 per cent of the patients with enlarged nerves showed decrease in size of the nerves and improvement of sensation. The general condition of the patients decidedly improved.

For a characteristically chronic disease, observation of new methods of treatment must cover a long time. These observations, it is hoped, will, when given the test of time, confirm the impression that in the administration of diphtheria toxoid and antitoxin a new method of treatment of leprosy is available which brings definitely beneficial results.

FRUMESS, Denver. [ARCH. DERMAT. & SYPH.]

ACTIVE IMMUNIZING EXPERIMENTS AGAINST MEASLES. K. PAPP, Orvosi hetil. **84**:260 (Sept. 28) 1940.

Infants of mothers who had measles in their infancy bring with them a diaplacental immunity. This immunity diminishes later. The author vaccinated the infants in the time of diminishing passive immunity with blood from persons with measles. The smallest doses which can cause measles in susceptible infants were

chosen. These doses do not cause any pathologic symptom in children who are in a stage of diminished passive immunity, but if they are repeated at certain intervals, the infants get an immunity which protects them against measles for a longer time, two to three years. These vaccinations were made on infants 4 months old. Four vaccinations were given at intervals of six weeks. Eighty children thus vaccinated were exposed to measles, and only 2 got the disease.

GÖTTCHE, Budapest, Hungary.

ACETONURIA IN CASES OF SCARLET FEVER. I. TELEGDI, Orvosi hetil. **84**:402 (Aug. 10) 1940.

It has been observed by numerous authors that acetonuria is often present in cases of scarlet fever and that there is some connection between acetonuria and the severity of the illness. Telegdi examined first 85 patients (children and adults) who had different illnesses but not scarlet fever and found that children are greatly inclined to have acetonuria; with Legal's method he found acetone in the urine in 42 per cent of the children with very different, even very mild illnesses. The acetone disappeared from the urine mostly in five days. Among the adults he could not find acetonuria in a single case. Four hundred and thirty-one patients with scarlet fever were observed; of these 100 had acetonuria and 331 did not. Among the children 20 per cent of those with mild scarlet fever and 30 per cent with the more severe form had acetonuria; the difference is therefore very slight. Among the adults 3.8 per cent of those with the milder form and 28 per cent of those with the more severe form had acetonuria. These examinations show that the acetonuria is of neither diagnostic nor prognostic value in cases of scarlet fever, especially in childhood.

GÖTTCHE, Budapest, Hungary.

DIAGNOSIS OF WHOOPING COUGH. O. GÖTTCHE, Orvosi hetil. **84**:417 (Aug. 17) 1940.

The methods of diagnosing whooping cough can be divided into two groups: (1) assisting methods (roentgen examination and blood picture) and (2) deciding methods (demonstration of Haemophilus pertussis, complement fixation and agglutination). The histopathlogic basis of whooping cough is a chronic interstitial pneumonia, as was shown by the author in 1929. This pneumonia shows characteristic changes on the roentgenogram. The essential roentgenographic change is the appearance of bilateral symmetric shadows which spread from the hili to the diaphragm, above which they broaden out. This picture was named by the author "basal triangle." The blood picture can be used for diagnosis only when the number of leukocytes is above 20,000 per cubic millimeter and the percentage of lymphocytes over 50 per cent. The presence of H. pertussis decides the diagnosis; this succeeds mostly only in the first two weeks of the illness. During this period the organism is found in 50 to 70 per cent of the cases. The complement fixation test can usually be used only after infancy, and positive reactions are obtained in 80 to 90 per cent of the cases in the fifth to the eighth week of the illness. The reaction to this test remains positive for fifteen months. In the epidemiology of whooping cough, adults play a much more important role than was thought earlier, not the adults with "first whooping cough" but those with "second whooping cough." These persons cough very little and for only a short time, but they can spread the illness, because the H. pertussis can be demonstrated in their expectoration.

GÖTTCHE, Budapest, Hungary.

FATE OF POLIOMYELITIC PATIENTS OF 1937 IN COPENHAGEN. A. MONBERG, Acta orthop. Scandinav. (nos. 3 and 4) **11**:184, 1940.

Monberg discusses the residual disabilities of 101 patients discharged to their homes one and a half to two years previously for further treatment of their paralytic poliomyelitis whose acute attack was sustained in 1937. During 1937 there were also 25 patients who died during an acute attack of the disease and

61 who had poliomyelitis of a nonparalytic form. The surviving 101 patients with the paralytic form are divided into three groups: (1) those with mild disability, who are functionally well, as the paralysis has subsided completely or left merely some slight defects of little inconvenience to ordinary physical activity; (2) those with moderate disability, whose functional capacity is lowered so that in order to earn their living or to do ordinary housework they must wear a supporting bandage or in whom transplantation of muscle or fixating operations on bones or joints were necessary to obtain stability of the paralyzed back or extremity, and (3) those with severe disability, who are incapacitated to such an extent that they are invalids in the legal sense of the term. On reexamination 58 patients are reckoned as having mild, 24 as having moderate and 19 as having severe disabilities. Reexamination shows that the mortality for the total material was 13.4 per cent and that complete disability in the legal sense of the term was the result in 10.2 per cent, while the remaining 76.4 per cent of patients were either fully restored or able to earn their living by working after treatment with stabilizing operations or supporting bandages.

J. A. M. A.

A Case of Fatal Postvaccinal Encephalitis. V. Sindbjerg Hansen, Ugesk. f. læger **102**:465 (May 2) 1940.

A girl of 5 years showed signs of encephalitis on the twelfth day after vaccination for smallpox and died three days later. Postmortem examination revealed extensive and intense degenerative changes in the brain. In Denmark there have occurred in all 12 cases of postvaccinal encephalitis, of which 6 ended fatally.

Wallgren, Göteborg, Sweden.

Casuistics of the Zoster-Varicella Problem. A. C. Drogendyk, Nederl. tijdschr. v. geneesk. **84**:2931 (Aug. 3) 1940.

The author describes 2 cases of herpes zoster, with the appearance of varicella in persons who had been in contact with these patients. In the surroundings of the patients no varicella occurred; so a relation between the zoster and varicella must be accepted with certainty.

van Creveld, Amsterdam, Netherlands.

Sulfanilamide Treatment of Twenty-Two Patients with Meningococcic Meningitis and Sulfanilamide and Sulfapyridine Therapy of Four Patients with Pneumococcic Meningitis. A. J. R. E. van Schoonhoven van Beurden and T. Loonstra, Nederl. tijdschr. v. geneesk. **84**:3673 (Sept. 21) 1940.

Of the patients with meningococcic meningitis treated by the authors from 1932 to 1938, 15 of 19 died. After the introduction of sulfanilamide treatment the mortality rate fell considerably, especially in very young patients. Of 8 patients 2 years old or less observed by the authors, only 2 died; of 8 adults, no less than 4. Although the doses of the sulfanilamide compounds given to these patients were only moderate, the writers are led to assume, from facts observed by them and from comparative considerations, that it is improbable that the fate of patients with meningococcic meningitis is solely determined by the amount of sulfanilamide given, so that a certain dosage does not warrant a success of this therapy. The prognosis of pneumococcic meningitis, even after the introduction of sulfanilamide treatment, remains a dubious one; of the 4 patients 3 died. The result of energetic treatment was a rather moderate one.

van Creveld, Amsterdam, Netherlands.

Acute Infectious Diseases

Prophylactic Use of Sulfanilamide in Rheumatic Subjects. Alvin F. Coburn and Lucille V. Moore, M. Clin. North America **24**:633 (May) 1940.

These authors state that in rheumatic subjects recrudescences of the disease follow and appear to result from hemolytic streptococcic infection of the upper respiratory tract.

In selecting children for this study of the effectiveness of sulfanilamide prophylaxis in the prevention of recrudescences, two prerequisites were sought: (1) that each subject had experienced frank attacks of rheumatic fever and (2) that each could be under close observation during the course of the study. Preference was given to those having had frequent or even annual attacks of the disease. Of the children selected, some were in institutions, some were attending classes for children with heart disease in New York schools and some were school children scattered through overcrowded tenements.

The drug was given three times a day, the total dose being 3 Gm. for most children and 2 Gm. for some of the smaller children. The blood levels were maintained at approximately 4 to 5 mg. per hundred cubic centimeters. About 10 per cent of the children had toxic symptoms within a few days. In some, these took the form of the classic sulfanilamide sickness; in others, in whom there had been recent rheumatic activity, a recrudescence occurred. Patients who tolerated the drug for two weeks had no further difficulty. Prolonged administration of sulfanilamide had no untoward effects except possible failure to gain weight in some instances.

In all, 184 children were kept under observation. They appeared to be almost completely protected against hemolytic streptococcic infection, and the incidence of rheumatic fever in the group was less than 1 per cent, against an expectancy of 35 per cent.

EUGENE SMITH, Ogden, Utah.

FULMINATING SONNE DYSENTERY: REPORT OF TWO CASES. R. T. COOKE, Brit. M. J. **2**:151 (Aug. 3) 1940.

The author reports 2 cases of Sonne dysentery. One patient was a girl 20 months of age, and the other was a girl 4 years of age, who died within twenty-four hours after being taken sick. He points out that the condition must be differentiated from cerebrospinal fever and poisonings and in smaller children from tetany of rickets. There is a brief review of the literature of similar cases. Otherwise the article does not lend itself to abstracting.

ROYSTER, University, Va.

RHEUMATIC FEVER. A. SCROGGIE, Rev. chilena de pediat. **11**:301 (June) 1940.

The author discusses rheumatic fever in childhood on the basis of the cases of 168 patients treated at the Hospital of Roberto Del Rio. Rheumatic fever in childhood must be treated at the earliest manifestation of symptoms and the slightest change from the normal in the heart.

The treatment he recommends consists in enforcement of rest for several months, with continued observation of the temperature and repeated determination of the sedimentation rate. Both the sedimentation rate and the temperature must have dropped to normal levels before the patient is permitted to get up or before the disease can be considered inactive.

During the active, or allergic exudative, period, salicylate is used by mouth and intravenously, alternated with high doses of aminopyrine if there is intolerance to the salicylate. All foci of infection must be eliminated, particularly adenoid vegetations, the tonsils and the appendix.

In the diet the author recommends diminution of chlorides and preponderance of vegetables and fruits, with a considerable reduction of meat. He also recommends establishment of a special clinic for treatment of patients with rheumatic disease and chorea complicated with heart disease. He points out the necessity for convalescent homes for these patients, since such homes allow prolonged control and observation.

SCHLUTZ, Chicago.

CHILDHOOD RHEUMATIC DISEASE IN CHILE. A. SCROGGIE, Rev. chilena de pediat. **11**:417 (July) 1940.

The author believes that rheumatic disease constitutes a medical social problem. He believes that it is a disease of domestication. In regions where the children

live in the free air and are not confined to overheated rooms, the disease does not appear.

If the diagnosis of the disease can be established during the first few days of the attack and aminopyrine is given, it is possible to avoid cardiac complications.

SCHLUTZ, Chicago.

ULCERATIVE STOMATITIS IN MALARIA. I. M. LIFSHITZ, Vrach. delo (no. 9) **22**:617, 1940.

The author points out that attacks of malaria are frequently associated with an ulcerative type of stomatitis. The lesions in question are always oval, vary from a few millimeters to about a centimeter in diameter, are surrounded by a hyperemic margin and are usually covered by a yellowish exudate, but present no infiltration. They occur most commonly on the mucosa of the lower lip and cheeks. The diagnosis is based on their occurrence at the time of the acute malarial paroxysm and their dramatic response to antimalarial therapy without any local treatment. The author believes that the ulcerative lesions follow the development of herpetic vesicles, the transformation, however, being so rapid that the herpetic stage is usually not seen. He believes also that the periodic occurrence of this type of stomatitis may thus be an aid in the diagnosis of latent or mild malaria.

BODER, Los Angeles.

Chronic Infectious Diseases

LATE CONGENITAL SYPHILIS: OBSERVATIONS UPON THIRTY-NINE PATIENTS OVER 25 YEARS OF AGE AT THE TIME OF FIRST ADMISSION. FRANK R. SMITH JR., Am. J. Syph., Gonor. & Ven. Dis. **24**:755 (Nov.) 1940.

In this paper the author lists the symptoms and physical observations of 39 patients with congenital syphilis over the age of 25 years. His explanation for the delay in diagnosis of congenital syphilis until such advanced age is that when these patients were infants, at the beginning of the century, the diagnosis of various lesions as syphilitic was less easily made than today. He states that in this series of cases 90 per cent of the objective signs of late congenital syphilis are found in or about the structures of the head. The three most frequent findings of these patients when first seen were Hutchinson teeth, interstitial keratitis or eighth nerve deafness. Other stigmas, such as saddle nose, perforation of the palate, periostitis and gummas, are also listed. The sex and race incidence was the same in this series as in any other reported series.

ROYSTER, University, Va.

THE INSTABILITY OF THE TUBERCULIN REACTION. W. DAHLSTROM, Am. Rev. Tuberc. **42**:471 (Oct.) 1940.

Several questions relating to the tuberculin reaction require further clarification. Among these Dahlstrom has selected the following for this study: Does the reaction once established by infection remain positive during the activity of the lesion? What is the character of the tuberculous lesions in the chest when variability in the reaction is found? There remains also the problem presented by the frequent absence of the reactions in patients showing calcified nodules presumably of tuberculous origin. Should reinfection occur in these patients who have lost their sensitiveness, positive reactions would then be due to the new infection rather than to the one which produced the calcified lesions.

The dispensary records of 3,919 members of five hundred and thirteen families were studied. The tuberculin reaction was positive in 2,490 persons in this group, and in 276, or 11 per cent, it passed from the positive to the negative state during the period of observation (five to fifteen years). However, in only 0.4 per cent of those having a 3 plus reaction to this first dose did the reaction later become negative, whereas a reversal of the reaction occurred in 70 per cent of 185 persons

who had given only a 1 plus reaction to the second dose. It was found that the greater the degree of family exposure the more likely was the reaction to remain positive.

In no case did the tuberculin reaction become negative in the presence of the active reinfection type of tuberculosis. In a small group in which the lesions were of a type diagnosed by roentgen ray examination only, including 2 cases of tuberculosis diagnosed as the active childhood type, 5 cases of the inactive or suspected reinfection type and 11 cases in which there was roentgenologic evidence of calcified childhood tuberculosis, the positive reaction became negative. The overwhelming majority of unstable reactors were children.

EUGENE H. SMITH, Ogden, Utah.

DEMONSTRATION OF TUBERCLE BACILLI. WILLIAM STEINKEN JR., Am. Rev. Tuberc. **42**:543 (Oct.) 1940.

A technic is described for sedimenting tubercle bacilli from urine, spinal fluid and other body fluids for culture smear and animal inoculation. The precipitating agent is an alcohol-precipitated protein from pleural fluid and white of egg. It is superior to tannic acid in that the sedimented protein is straw colored and does not interfere with the color change of the indicator used for adjusting the p_H and does not inhibit the growth of tubercle bacilli.

EUGENE H. SMITH, Ogden, Utah.

PRIMARY MASSIVE PULMONARY TUBERCULOUS INFECTION IN AN INFANT, WITH RECOVERY. G. POZZI, Med. ital. **21**:205 (May) 1940.

The author reports the case of an infant who showed an extensive pulmonary tuberculous infection at the age of 13 months but had recovered by the age of 4 years. Roentgen examinations were used to follow the course and show the recovery.

MARTOCCIO, Utica, N. Y.

SYPHILIS AS A FACTOR IN INFANTILE ENCEPHALOPATHIES. J. D. LUQUE, Rev. chilena de pediat. **11**:317 (June) 1940.

In the material reported by the author syphilis was present in about 45 per cent of the cases. It was not always clear whether it was the causal agent or whether it was merely coincidental. It is important to recognize its presence in cases of encephalopathy in connection with the treatment.

SCHLUTZ, Chicago.

INCIDENCE, COURSE AND TREATMENT OF PRIMARY TUBERCULOSIS OF OLDER SCHOOL CHILDREN AND YOUTHS. A. VIETHEN, Ztschr. f. Kinderh. **62**:80 (Aug. 9) 1940.

Tuberculin tests of the entire population of two villages revealed that only 32 per cent of all school children and only one third of all youths up to 20 years of age had been infected. The delay in infection has as a consequence a greater incidence of infection just before and after puberty.

Seven cases are discussed in detail, and six roentgenograms are shown. Infiltrations, especially rounded shadows, are common. Pleural effusion also plays a noteworthy role.

The prognosis in general is good, but superinfection and the hormonal influences of puberty must be kept in mind.

Treatment consists mainly in prolonged rest during the acute stage.

SIEMSEN, Chicago.

TUBERCULOUS FOCI IN BONE. G. ODELBERG-JOHNSON, Nord. med. **6**:1084 (June 22) 1940.

The hematogenous tuberculous focus is caused by a bacterial embolus in a bone marrow artery. The marrow which is thus damaged by toxin is replaced

by tuberculous granulation tissue, and the osseous trabeculae are necrotized. Such a tuberculous focus in bone has usually a great tendency to spontaneous demarcation. Its localization in the skeleton may cause the following complications: perforation into a joint, with secondary arthritis; dislocation of functionally important skeletal parts, such as the vertebral columna; formation of abscesses and fistulas, involving risk of secondary infection. The sites of predilection are spongy bone regions rich in blood vessels. Foci in long bones are diaphysial, metaphysial (children) or articular (adults). The frequency is greatest in small spongy bones, such as the tarsal bones, pelvis and vertebral bodies. In flat bones, with their scarce spongy substance, foci are less common. The tuberculous bone focus is a symptom of the tuberculous infection, its prognosis depending on the prognosis of the latter. The treatment must therefore above all be directed against the general tuberculous disease. The local disease should first be treated by elimination of weight bearing and by fixation. In the absence of perforation into a joint or dislocation, an attempt at radical excochleation without damaging the continuity of the bone is indicated. This should be done when the general state of health is optimal and the activity of the tuberculosis at a minimum. The usual result is restoration, in some cases with invalidism.

WALLGREN, Göteborg, Sweden.

INCIDENCE OF BOVINE TUBERCULOSIS IN NORWAY. FRANCIS HARBITZ, Tidskr. f. d. norsk. lægeforening. **60**:463 (June 15) 1940.

In 1895 8 per cent of the tested cows gave positive tuberculin reactions. In 1915 only 5 per cent gave positive reactions. In 1915-1927 the milk of 564 cows without known tuberculosis of the mammary gland was examined for tubercle bacilli, with positive results in 3 cases. The author is of the opinion that bovine tuberculosis in Norway in a few years will be eradicated.

WALLGREN, Göteborg, Sweden.

SYPHILIS OF THE SECOND GENERATION. OLAV IDSOE, Tidskr. f. d. norsk. lægeforening. **60**:995 (Dec. 1) 1940.

A male newborn infant had pemphigus syphiliticus on his hands and feet, rhinitis, osteochondritis and a positive Wassermann reaction. The mother had been treated at the age of 12 years for a syphilitic chorioretinitis and parenchymatous keratitis (positive Wassermann reaction). The grandmother of the boy had been infected by her husband.

WALLGREN, Göteborg, Sweden.

PULMONARY TUBERCULOSIS WITH PERFORATION OF TUBERCULOUS GLANDS INTO THE BRONCHI, TRACHEA AND ESOPHAGUS. P. NIEUWENHUYSE, Nederl. tijdschr. v. geneesk. **84**:4354 (Nov. 9) 1940.

In this clinical lecture a short clinical report and a more extensive pathologic description are given of an extraordinarily rapid and malign form of tuberculosis observed within a short time in 3 children of one family. Tubercle bacilli of the bovine type were found in these cases. In all 3 children the disease had a similar course. There existed extensive caseations and liquefactions with cavity formation in both lungs, and perforation of tuberculous glands into the bronchi and esophagus had taken place. The similarity of the changes found in all 3 cases probably must be explained in this way: The children were infected for the first time with tubercle bacilli, which invaded the lungs and spread along the lymph channels very quickly owing to the malignity of the process. The cause of this malignity is sought not in the lack of immunity but in an unusual virulence of the bacilli. (See also Hoeden, J. van der: Interhuman Contagion with Bacillus Tuberculosis of the Bovine Type, *Nederl. tijdschr. v. geneesk.* **84**:4390 [Nov. 9] 1940.)

VAN CREVELD, Amsterdam, Netherlands.

INTERHUMAN CONTAGION WITH BACILLUS TUBERCULOSIS OF THE BOVINE TYPE. J. VAN DER HOEDEN and M. F. DE RAADT, Nederl. tijdschr. v. geneesk. **84**:4390 (Nov. 9) 1940.

In a family of 6 children and healthy parents 3 children died of tuberculosis after a brief illness. The clinical course and pathologic observations showed a remarkable agreement; in all 3 children tubercle bacilli of the bovine type were found. Patient A, a girl of 16 years, had probably been infected by contact with a cow suffering from open pulmonary tuberculosis. In a period in which she expectorated much infective material, she slept one night with 2 children (a girl of 15 and a boy of 10 years), who fell ill simultaneously two months later and died after another two months. In a fourth child (a girl of 12 years), who had likewise slept one night with patient A, tubercle bacilli were found in the stomach washings, which also showed cultural properties of bovine bacilli but which were not tested for virulence. This girl had a patchy pulmonary pattern and broadened hilar shadows, but clinically she was not ill. (See also Nieuwenhuyse, P.: Pulmonary Tuberculosis with Perforation of Tuberculous Glands into Bronchi, Trachea and Esophagus, *Nederl. tijdschr. v. geneesk.* **84**:4354 [Nov. 9] 1940.)

VAN CREVELD, Amsterdam, Netherlands.

Diseases of Blood, Heart and Blood Vessels and Spleen

FREQUENCY OF MONONUCLEOSIS INFECTIOSA. E. ØLLGAARD, Nord. med. **6**:671 (April 6) 1940.

Examination of the blood of 1,816 patients admitted to a hospital for diphtheria, suspicion of diphtheria or tonsillitis were carried out in order to get an impression of the frequency of infectious mononucleosis. The disease was diagnosed in 210 cases, all of them sporadic cases. In 1 case the period of incubation could be determined as four days. Fifty per cent of the patients were between 15 and 24 years of age. In males the frequency was greater below 15 years and in females above this age. In 22 per cent of the cases the false membranes in the fauces were so extensive that antidiphtheria serum would have been given had not the condition been correctly diagnosed as infectious mononucleosis. All the patients recovered. The number of leukocytes varied from 3,000 to 27,000; in 1 case the count was 51,000. More than 40 per cent of the cells were mononuclear, and in addition there were 14 to 68 per cent atypical cells. Bunnell's test was carried out in 76 cases. Its diagnostic value seems to be greatest for patients above 14 years of age (75 to 83 per cent positive results). In patients 0 to 4 years of age there were no reliable reactions. In the group 5 to 9 years old there were 30 per cent positive reactions, and in the group 10 to 14 years old, 58 per cent.

WALLGREN, Göteborg, Sweden.

ARTERIAL ANEMIA IN CHILDREN. BERTIL HAMNE, Nord. med. **6**:905 (May 11) 1940.

The symptoms of arterial anemia are abnormal psychic and physical fatigue and fatigability, a feeling of pressure bearing down on the head, and also headache, backache, diffuse stomach trouble or ulcer-like discomfort, cardiac palpitation and often orthostatic albuminuria. All these symptoms need not necessarily appear in a single patient. These disturbances are likely to develop in a tall, thin person as a result of standing or sitting for a long time and are due to an abnormal displacement of blood from the upper to the lower parts of the body. When the patient is standing the diaphragm falls abnormally and the heart becomes drop shaped, decreasing more than normally in volume. Among the things familiar to pediatricians is an increase in pulse rate of 20 beats or more per minute arising from a child's maintaining a standing position. This occurs simultaneously with a decrease of the systolic blood pressure. The author emphasizes the importance of the school physician and teacher devoting special attention to these children, who are often misjudged as backward and inattentive at school. All the troubles

disappear if the patient gains in weight at the same time as the abdominal muscles are strengthened. A well balanced diet, one hour's rest in the horizontal position after the principal meal, gymnastics (repeated lifting and lowering of the legs in the recumbent position) and wearing of an abdominal support are recommended.

WALLGREN, Göteborg, Sweden.

A CASE OF SURGICALLY TREATED SO-CALLED THROMBOSIS OF THE SPLENIC VEIN. KURT G. KAIJSER, Nord. med. **6**:978 (May 25) 1940.

A boy born in 1934 in February 1936 had hemorrhagic vomiting with secondary anemia (hemoglobin 37 per cent), and slight transitory splenomegaly occurred. He was again examined in 1938, at 4 years of age. He then had a hemoglobin content of 40 per cent. The spleen was not palpable. After a blood transfusion, bloody stools were noted for a few days, and some days later, after another transfusion, hematemesis occurred. The melena and the hematemesis were repeated once. Roentgenologically, esophageal venectasia was demonstrable. The spleen was enlarged. Ascites was not present. The liver was normal. The boy was splenectomized and discharged well. No thrombosis was found in the principal lienal vein, but one of the vessels of the splenic hilus was obstructed. The spleen was somewhat sclerosed and greatly enlarged (weight 140 Gm.).

WALLGREN, Göteborg, Sweden.

SEVERE ANEMIA AFTER TREATMENT WITH SULFAPYRIDINE. PER ROSENBERG, Tidskr. f. d. norsk. lægeforening. **60**:72 (Jan. 15) 1940.

The author reports the cases of 2 children, 9½ and 3 years of age, who had previously been under treatment for secondary anemia. After sulfapyridine was given, in treatment of an acute infection, severe anemia without leukopenia developed, which in the first case ended fatally and in the second case was cured by blood transfusions.

WALLGREN, Göteborg, Sweden.

TREATMENT OF INFECTIOUS MONONUCLEOSIS WITH TRANSFUSION OF CONVALESCENT BLOOD. H. C. A. LASSEN and S. THOMSEN, Ugesk. f. læger **102**:774 (July 25) 1940.

In 12 cases of infectious mononucleosis intravenous treatment with specific convalescent serum (60 to 300 cc.) caused a rapid improvement of the general condition of the patients. The temperature in most cases fell to a normal level within twenty-four to forty-eight hours.

WALLGREN, Göteborg, Sweden.

THE INFLUENCE OF EXTIRPATION OF THE SPLEEN ON THE BLOOD PICTURE. A. W. C. G. KAMERLING and P. H. M. DE ROO, Nederl. tijdschr. v. geneesk. **84**:2643 (July 13) 1940.

The influence of extirpation of the spleen on the blood picture was studied in some patients operated on for rupture of the spleen. The blood picture was also examined in 1 patient six years after a splenectomy performed because of (probable) thrombosis of the splenic vein and in another patient eleven and three-fourths years after a splenectomy done because of a sarcoma of the spleen. Several of the signs described in the literature, such as a transitory normoblastic crisis, Jolly bodies and thrombocytosis, were found. The changes of the white blood picture are very variable. In connection with the splenectomy, an enlargement of the mean diameter of the erythrocytes up to 9 microns was observed. This considerable enlargement was transitory, but in all studied cases for many years after the operation a moderate increase was still found. In 2 rabbits after removal of the spleen a transitory increase of the diameter of the erythrocytes was found, blocking the reticuloendothelial system with colloidal copper solution or chinese ink appeared to be without any influence on the size.

VAN CREVELD, Amsterdam, Netherlands.

Diseases of the Gastrointestinal Tract, Liver and Peritoneum

THE AMYLOLYTIC AND PHOSPHATASE ACTIVITY OF LIVER TISSUE IN VON GIERKE'S DISEASE. S. J. THANNHAUSER, S. Z. SORKIN and N. F. BONCODDO, J. Clin. Investigation **19**:681 (July) 1940.

The presence of amylolytic activity in liver tissue involved by von Gierke's disease was corroborated. The alkaline phosphatase activity of the liver tissue in 3 cases of glycogen storage disease was found to be significantly lower than that present in normal livers of 2 children.

GUEST, Cincinnati.

TREATMENT OF VOMITING OF THE ACETONEMIC TYPE BY INTRAMUSCULAR INJECTIONS OF EXTRACT OF CYNARA. LEON TIXIER, Arch. de méd. d. enf. **43**:207 (July-Aug.) 1940.

In 1936, Tixier first pointed out the advantages of artichoke in stimulating hepatic-renal functions in the infant.

While but 1 patient with hepatic insufficiency, a boy of 4 years, was observed, patients with crises of vomiting and the presence of acetone in the urine were encountered at least three times a year. In these patients the area of hepatic dulness was of twice the normal extent. A single course of treatment continuing for ten days with injection of 0.2 Gm. of an extract of cynara three times daily gave gratifying results; normal digestion returned, vomiting and acetonuria disappeared, the volume of the liver reached normal limits and the body weight was increased 2 Kg. in ten months. The author reports a series of cases with minute observations on the clinical progress.

AMESSE, Denver.

MALFORMATIONS OF THE DIGESTIVE TRACT. MARIANO PACHECO and SANTOS LUIS CRESPI, An. Soc. puericult. Buenos Aires **6**:123 (April-June) 1940.

Three cases of malformation of the intestinal tract are reported. In case 1, Oswaldo a few hours after birth was given sugar water, which he continued to vomit each time it was offered. In case 2, Mario M., on the second day nursed well; in the afternoon there occurred fecal vomiting. In case 3, Juan C., on the second day took breast feeding well but a few minutes after nursing ejected a greenish vomitus. It is not possible to say that a newborn infant is perfectly formed, in spite of a good external appearance, until it is known that his functions are perfect. Oswaldo began vomiting on the first day, but our other 2 patients gave no suspicion of malformation of the intestinal tube. Moreover, in the case of Oswaldo vomiting occurred at once after he took food, owing to an obstruction at the distal end of the ileum; Juan C.'s vomiting bore no relation to the taking of food but his vomitus was bile stained, as the obstruction was at the lower end of the duodenum. Another point to be considered is the relation of the condition to the peculiarities of the intestinal evacuations. Mario M. and Juan C. both passed plugs of meconium. For the clinician these points are of interest, as they permit a better interpretation of the cases.

GIFFEN, Toledo, Ohio.

HEMATEMESIS IN AN INFANT OF ELEVEN MONTHS. H. MAGLIANO, T. SLECH and H. J. MANARA, An. Soc. puericult. Buenos Aires **6**:129 (April-June) 1940.

A boy aged 11 months, in good general condition, without syphilis or tuberculosis, with no hemorrhagic tendency and with no roentgenographic or clinical lesions of the gastrointestinal tract, nevertheless has a pure hematemesis and repeatedly vomits bloody fluid. A diagnosis of duodenal ulcer has been made by prominent physicians. The authors disagree with this.

It is true, according to Finkelstein, that hematemesis with melena is a pathognomonic sign of gastric ulcer. This condition, however, is extremely rare in infancy. The sources of hematemesis are listed: (*a*) swallowed blood, (*b*) blood dyscrasia, (*c*) hepatitis, (*d*) thrombophlebitis of the portal system, (*e*) hemorrhagic gastritis in the submucosa, (*f*) gastric ulcer, (*g*) duodenal ulcer and (*h*) esophageal varices.

The authors are opposed to laparotomy, and statistics are cited showing this operation to have a mortality of 100 per cent. Rest and application of ice are advised. Considering the good condition of the patient, the authors' treatment has consisted of waiting and, as medication, administration of calcium gluconate and of ultraviolet ray baths.

Up to the time of the report there had been no vomiting or hematemesis.

GIFFEN, Toledo, Ohio.

INTESTINAL INFECTION BY SALMONELLAS. VICTOR ZERBINO, A. RAMON GUERRA and P. L. ALEPPO, An. Soc. puericult. Buenos Aires **6**:134 (April-June) 1940.

Animal salmonellosis is not a rare and accidental infection but is extensive and common.

In the children observed by the authors, enteritis and diarrhea caused by salmonella infection constitute 41.9 per cent of enteritis and 12.56 per cent of all diarrhea. The frequency is 95.9 per cent in early infancy and 66.4 per cent in the first year of life.

The disease is contagious in children.

The period of incubation is one to two days. The malady begins brusquely. Gastrointestinal symptoms consist of: anorexia, vomiting, diarrhea with orange-colored serous feces; mucus, pus and blood in the mucous membrane; colics, straining and tenesmus; a distended and somewhat pasty abdomen, and enlargement of the liver and at times of the spleen. There are poor nutrition, dehydration, acidosis, circulatory disturbances and at times atrophy. Fever is the important infectious symptom. Toxic symptoms include evidence of damage of the liver and kidney and disturbances of the central nervous system.

The prognosis depends on the age and the clinical form, serious complications occurring even with mild forms of the disease.

Besides sulfapyridine therapy, dietetic regimens were used, and efforts were made to give symptomatic treatment. Infants regarded as dying were cured.

GIFFEN, Toledo, Ohio.

TREATMENT OF RECTAL PROLAPSE IN THE CHILD BY PROTEIN THERAPY. J. M. JORGE and A. GRECO, Arch. argent. de pediat. **14**:223 (Sept.) 1940.

The treatment of rectal prolapse in children constitutes an important chapter in daily pediatric practice. The authors have treated patients with this condition for the past thirteen years, with good results, by injections of protein into the inferior rectal wall. The injection of protein stimulates the muscular tissue of the sphincter. This stimulation brings about a hyperemia, which in turn reestablishes muscular tone.

Prolapse appears commonly during diarrhea or in the course of enteral colitis or habitual constipation. The children usually are neuropathic or are troubled with persistent cough. At times rectal polyps may be the cause.

In the majority of cases there are considerable muscular dystrophy and chronic dehydration. Injection of protein offers a fairly painless treatment with assurance of good results. It can be carried out under local or general anesthesia. No shock or unfavorable anaphylactic symptoms have been encountered.

SCHLUTZ, Chicago.

HOW DOES BACTERIUM BIFIDUM (TISSIER) ENTER THE INTESTINAL TRACT? GRETE STOELTING, Monatschr. f. Kinderh. **83**:83, 1940.

Bacterium bifidum belongs to the Corynebacteria and pronounced anaerobic organisms. The Blaurock plate was used as a culture test after the Fortner method. It is found in the stool of normally nourished babies regularly by the third day after birth. Otherwise it has only been found in decayed teeth.

Infection through the blood of the mother may be rejected as highly improbable.

Oral infection cannot be proved, as tests have failed to reveal the organism in women's milk, on the mamilla or in the cavity of the mouth of a newborn child. Bacterium bifidum being nonmotile, infection per anum does not come into consideration.

One may suppose that there is a possibility of some relation between Bact. bifidum and Bacterium amylobacter.

NEURATH, New York.

TREATMENT OF MELENA WITH VITAMIN K. H. WILLI, Monatschr. f. Kinderh. **83**:347, 1940.

Five infants with melaena vera and 2 with umbilical hemorrhages were successfully treated with vitamin K. The vitamin not only brought about a surprisingly speedy decrease of the prothrombin time but also decreased the time of coagulation in general. Former methods of treatment had no such effect.

NEURATH, New York.

TWO CASES OF DIAPHRAGMATIC HERNIA. O. SCHUBERTH, Nord. med. **7**:1196 (July 6) 1940.

Case 1.—A boy of 5 years, previously healthy, fell suddenly ill with abdominal pains. Laparotomy revealed a normal appendix, stomach, descending colon, liver and gallbladder. A roentgenogram taken several days later revealed a diaphragmatic hernia on the left side. The greater portion of the small intestine, transverse colon and cecum were displaced into the left pleural cavity. The boy was successfully operated on and discharged well.

Case 2.—A boy of 15 was admitted to the hospital with the diagnosis of appendicitis and situs inversus. Roentgenograms showed a diaphragmatic hernia (on the left side) containing the small intestine and the colon. Operation was performed, and the patient was discharged well.

WALLGREN, Göteborg, Sweden.

CASE OF FAMILIAL CIRRHOSIS OF THE LIVER. V. ESKELUND and ERIK WARBURG, Nord. med. **7**:1228 (July 13) 1940.

The authors report a case of familial, presumably congenital, cirrhosis of the liver in a girl 11 years old. A brother of the patient died at the age of 6 of an illness with similar morbid features. This is the first case of its kind described in Denmark. According to the clinical and pathologic observations, this girl had one of the rare examples of cirrhosis developing predominantly like the Laennec type, with a relatively protracted initial period and a very rapid terminal progression.

WALLGREN, Göteborg, Sweden.

TREATMENT OF ACUTE INTUSSUSCEPTION IN CHILDREN. JAMES HINDMARSH, Nord. med. **7**:1433 (Aug. 24) 1940.

In 1930 to 1934, 24 patients with intussusception were treated conservatively by attempts to reduce the intussusception by enema under fluoroscopic control. If this method was found unsuccessful laparotomy was performed. The mortality rate was 16.7 per cent. In 1935 to 1939, 42 patients were primarily treated surgically, with a mortality rate of 2.4 per cent.

WALLGREN, Göteborg, Sweden.

HEPATITIS WITHOUT JAUNDICE. NIELS SVITH, Ugesk. f. læger **102**:915 (Sept. 5) 1940.

The author gives a brief report on 27 patients displaying symptoms similar to those prevalent in catarrhal jaundice but without jaundice, bilirubinemia and bilirubinuria. On the basis of results of tests of hepatic functions, a hepatitis is suggested as the cause of these symptoms.

WALLGREN, Göteborg, Sweden.

ULCERATIVE COLITIS FROM A SURGICAL POINT OF VIEW. A. WELCKER, Nederl. tijdschr. v. geneesk. **84**:1400 (April 13) 1940.

With the observations in 19 cases of ulcerative colitis, a detailed discussion is given of the course and treatment of this condition. Treatment is more efficient when instituted early. It should consist in regular colonic lavage from an appendicostomy or cecal fistula; this treatment can be carried out by the patient himself without interference with his working capacity. In almost 75 per cent of the cases observed a good result was obtained in this way and the opening could eventually be closed. It is only when this treatment is a failure after regular and prolonged application that more radical methods have to be considered, such as total exclusion of smaller or larger sections of the colon by a preternatural anus. This treatment eventually leads to the removal of a larger or smaller portion of the colon or rectum. It has the disadvantage of making the patient incapable for work for a long time. VAN CREVELD, Amsterdam, Netherlands.

OXYURIS AND APPENDICITIS. J. SCHWARZ and M. STRAUB, Nederl. tijdschr. v. geneesk. **84**:1627 (April 27) 1940.

The authors arrive at the following conclusions:

1. Oxyuris is often found in the appendix, especially in young persons.

2. The worm regularly causes characteristic lesions of the epithelium and of the mucosa.

3. When the parasite penetrates into the deeper layers of the wall of the appendix it causes abscess formation and the same reaction as a foreign body. Encapsulation and calcification follow.

4. The reactionless immigration of the worm into the wall of the appendix described by most authors is a postvital process.

5. Oxyuris is often found in appendixes with signs of purulent inflammation.

6. The opinion of Brumpt (1927) and of Rheindorf (1921) that Oxyuris is an important primary cause for appendicitis and that therefore an antioxyuris campaign would be of social importance deserves serious consideration.

VAN CREVELD, Amsterdam, Netherlands.

HYPERTROPHIC PYLORIC STENOSIS IN ADULTS. J. F. NUBOER, Nederl. tijdschr. v. geneesk. **84**:1687 (May 4) 1940.

Two cases are described of hypertrophic pyloric stenosis in adults. In a woman of 30 with a history of gastric trouble for four years, besides muscular pyloric stenosis only gastritis was found. The anatomic picture greatly resembled that of the pylorus in pyloric hypertrophy of babies. The muscle fibers on microscopic examination showed a vacuolar structure, and the vacuoles probably contained glycogen. The second case was that of a man of 36 who had had frequent vomiting since childhood but only for the last four years had had typical symptoms of ulcer. In addition to muscular pyloric hypertrophy, two small ulcers were found on the lesser curvature. In view of the facts found in the literature, the opinion is held that the condition is congenital. For any form of pyloric hypertrophy in adults gastric resection is recommended.

VAN CREVELD, Amsterdam, Netherlands.

Nervous Diseases

TREATMENT OF PNEUMOCOCCIC MENINGITIS. RICHARD G. HORSWELL, WILLIAM H. REALS, WAYNE W. FOX, PAUL S. RHOADS, ARCHIBALD L. HOYNE and BENJAMIN LEVIN, J. A. M. A. **115**:917 (Sept. 14) 1940.

In 22 consecutive cases of pneumococcic meningitis treated with type-specific serum and sulfanilamide or sulfapyridine there were 7 recoveries. There were

only 2 recoveries at the Cook County Hospital in the years previous to the introduction of chemotherapy. Pneumococcic meningitis has become more common there than meningococcic meningitis. As soon as the diagnosis of meningitis is made, administration of sulfapyridine or of its sodium salt is started, and the organism is identified or typed as soon as possible. Then the serum is administered intravenously. The concentration of the drug in the blood is checked, and anemia and leukopenia are treated by blood transfusion. Surgical drainage of infections foci is mandatory and patients with complications have a poorer prognosis.

HEERSMA, Kalamazoo, Mich.

TUBERCULOMA OF THE BRAIN IN CHILDHOOD. I. W. CAMERER, Monatschr. f. Kinderh. **83**:163, 1940.

Camerer describes 2 cases of tuberculoma of the brain in infants and discusses the frequency, localization, diagnosis and prognosis of the disease, particularly its roentgenologic differentiation from calcification.

NEURATH, New York.

PATHOGENESIS OF HYDROCEPHALUS IN SPINA BIFIDA. OLOF ASK, Nord. med. **7**:1232 (July 13) 1940.

The author has made an anatomic study of 4 cases of noninfected spina bifida. He calls attention to a repression of the differentiation of the meninges, meninx primitiva persistens, occurring in spina bifida. This repression, which causes conditions similar to those resulting from postmeningitic adhesions of the leptomeninges, may be a cause of the hydrocephalus in cases of spina bifida.

WALLGREN, Göteborg, Sweden.

PNEUMOCOCCIC MENINGITIS FOLLOWING OTITIS MEDIA, HEALED AFTER A RAMADIER OPERATION AND TREATMENT WITH SULFAPYRIDINE AND SPECIFIC ANTIPNEUMOCOCCUS SERUM. P. G. GERLINGS and C. M. KRÖGER-WIBAUT, Nederl. tijdschr. v. geneesk. **84**:1494 (April 20) 1940.

In a girl of 10 years acute otitis media with petrositis developed into pneumococcic meningitis. On operation by the method of Ramadier pus was found in a cavity in the apex of the petrous bone. After the operation high daily doses of sulfapyridine were given, after which the general condition improved, the temperature settled down and the fluid became sterile. From the sixth day after the operation the condition became worse again; the temperature rose and pneumococci again appeared in the fluid. Continued sulfapyridine treatment could not modify the condition. After addition to the treatment of daily intravenous doses of 20,000 units of specific antipneumococcus serum for four days, the patient recovered within a short time. The combination of chemotherapy and serum in the treatment of pneumococcic meningitis is commented on.

VAN CREVELD, Amsterdam, Netherlands.

PARALYSIS OF CONTRALATERAL ABDUCENS NERVE IN OTOGENIC MENINGITIS. W. J. POTHOVEN, Nederl. tijdschr. v. geneesk. **84**:2238 (June 15) 1940.

The author reports on 2 patients, 13 and 19 years old, who recovered from an otogenic meningitis complicated by a paralysis of the contralateral abducens nerve two and eighteen days respectively after the operation on the ear. The abducens nerve healed without any further surgical measures. Homolateral and contralateral paralysis of the abducens nerve in the course of infections of the ear are discussed.

VAN CREVELD, Amsterdam, Netherlands.

Diseases of the Genitourinary Tract

NOCTURNAL ENURESIS: EXPERIENCES WITH EVACUATED CHILDREN. SAMUEL E. GILL, Brit. M. J. **2**:199 (Aug. 10) 1940.

The author describes his experiences and information gained from investigation of 140 children suffering with enuresis after being evacuated from their homes in London and Croydon. He was able to obtain fairly accurate records on 97 of these children. His summary and conclusions are as follows:

"Among ninety-seven bed-wetting children evacuated from London and Croydon to Brighton as a war measure, particulars of whose cases have been obtained, there does not appear to be any special connexion between the housing condition (considering the areas from which they come), the presence or absence of regular work of the father, or other general condition under which the children have lived, and their enuresis. It is suggested that the common factor for practically all, if not all, is a low social standard on the part of the parents, probably inherited.

"Two-thirds of the children are below the average in their school attainments.

"The number of cases cured by their being placed in good home conditions with foster-parents is very small indeed.

"There is a tendency for them to relapse after a month and for the nocturnal to be replaced by diurnal incontinence.

"Incontinence has been found to be present in evacuated children of all ages from the youngest to the oldest."

ROYSTER, University, Va.

RENAL ALTERATIONS IN CASES OF CHLOROPRIVIC UREMIA. Ö. KERPEL-FRONIUS and R. MARTYN, Orvosi hetil. **84**:319 (May 25) 1940.

It is well known that in illnesses in which the organism loses much salt there develops a pathologic picture characterized by severe dehydration, circulatory and respiratory disturbances and increase of nonprotein nitrogen in the blood. This state is named chloroprivic uremia. Milder forms can be cured by administration of physiologic solution of sodium chloride. Postmortem examination in cases of such mild forms did not show any pathologic alterations in the kidneys; therefore, it was thought at first that the whole pathologic picture was of extrarenal or functional origin. Later, however, necrobiotic changes, fatty degeneration and even calcification were found in the kidneys in cases of chloroprivic uremia. Authors investigated the causes of these anatomic changes by animal experiments and came to the conclusion that milder alterations can be explained by anhydremia or circulatory disturbances but that calcification develops only when severe salt deficiency is accompanied with pronounced alkalosis.

GÖTTCHE, Budapest, Hungary.

CARBUNCLE OF THE KIDNEY. L. D. EERLAND, Nederl. tijdschr. v. geneesk. **84**:1386 (April 13) 1940.

A classic case of carbuncle of the kidney in a girl of 14 years is described. The etiology, differential diagnosis and therapy of this condition are discussed as well as many features which the clinical picture may show.

VAN CREVELD, Amsterdam, Netherlands.

CYSTINURIA AND RENAL DWARFISM, COMBINED WITH PYRAMIDAL AND EXTRAPYRAMIDAL SYMPTOMS. M. O. VAN DER ZYL and E. M. HESLINGA, Nederl. tijdschr. v. geneesk. **84**:2120 (June 8) 1940.

The authors describe a case of renal dwarfism in a boy, now 12 years old, combined with cystinuria and pyramidal and extrapyramidal symptoms. The authors believe, with Gordh (1939), that diencephalic lesions are of great etiologic importance but that a pathoplastic influence of eventually existing congenital uropoietic anomalies cannot be excluded.

VAN CREVELD, Amsterdam, Netherlands.

TREATMENT OF RETENTIO TESTIS. R. J. HARRENSTEIN, Nederl. tijdschr. v. geneesk. **84**:2332 (June 22) 1940.

In view of the results obtained with endocrine and surgical treatment in retention of the testes, as compared with the effect of a purely expectant attitude, the question is discussed whether this developmental abnormality should be treated at all, and if it should, which treatment is preferable. The author's observations on patients with bilateral retention who were operated on for release of one testis only showed that waiting for the descent of the testicle into the scrotum during and after puberty involves a risk of insufficient development of the organ. As the most suitable age for treatment for most patients the approach of puberty should be chosen.

VAN CREVELD, Amsterdam, Netherlands.

Diseases of the Ductless Glands; Endocrinology

ALKALOSIS AND LOW PLASMA POTASSIUM IN A CASE OF CUSHING'S SYNDROME: A METABOLIC STUDY. DONALD M. WILLSON, MARSCHELLE H. POWER and EDWIN J. KEPLER, J. Clin. Investigation **19**:701 (Sept.) 1940.

Plasma electrolytes and the metabolic balances of potassium, chlorine, sodium and nitrogen were studied in a man, 39 years of age, with Cushing's syndrome. In the plasma there were a diminished concentration of potassium and chlorine, increased bicarbonate, an elevated p_H, and normal concentrations of sodium, protein, calcium, magnesium, phosphorus and sulfates, and undetermined acid fraction. It was suggested that the abnormal distribution of plasma electrolytes was the result of the failure of the kidney to retain potassium. The pattern of the plasma electrolytes returned to normal after simultaneous administration of potassium chloride and ammonium chloride, but the continued administration of potassium chloride apparently did not influence the course of the disease.

GUEST, Cincinnati.

DEVELOPMENT OF LIPODYSTROPHY IN DIABETES FOLLOWING INSULIN THERAPY. M. L. SALDUN DE RODRIGUEZ, Arch. de pediat. d. Uruguay **11**:642 (Aug.) 1940.

The author describes 3 cases of lipodystrophy. In 2 of them the condition was of the circumscribed type occurring in the area in which the injections of insulin were generally given.

The author describes the various theories advanced as to the causation of this type of dystrophy, among them the possibility that it is due to the antiseptics which are added to insulin, such as tricresol, or to the action of the protamine zinc type of insulin. Another theory ascribes it to the concentration of the insulin used.

As a prophylactic measure the author advises frequent change of the location of the injection. Diabetic patients tend to use the same area for injections continually because sensibility in such an area seems to diminish.

SCHLUTZ, Chicago.

PROGNOSIS OF DIABETES IN CHILDREN. PER SELANDER, Svenska läk.-tidning. **37**:1288 (Aug. 9) 1940.

A check-up was made on 155 of a series of 156 diabetic children treated with insulin in the years 1920 to 1939. The missing patient was still living and earned his livelihood as a circus artist. The youngest child in whom diabetes developed was 10 months old. Twenty-seven of the children had died (17.4 per cent), 17 from diabetes and the others from acute or chronic infections. The annual mortality rate was 0.5 to 1.5 per cent. The author stresses the fact that the risk of tuberculosis increases as the patient attains puberty. Nine patients were found

to have acquired clinical tuberculosis; 4 of these had died. Among other diseases may be mentioned acute hepatitis in 24 cases. In 6 cases the physical development was delayed.

WALLGREN, Göteborg, Sweden.

Diseases of the Muscles, Bones, Joints and Lymph Glands

MYOTONIA CONGENITA (THOMSEN), WITH SPECIAL REFERENCE TO SYMPTOMS IN INFANCY. WOLFGANG KIEHL, Arch. f. Kinderh. **118**:79 (Oct. 27) 1939.

The characteristic symptom of this disease is a peculiar rigidity of the muscles at the beginning of a movement after a rest period. The irritability to mechanical and electrical stimuli is increased. The contraction persists much longer than the duration of the stimulus.

The author describes a new early symptom which allows one to detect the disease regularly even in very young infants. This symptom, caused by a myotonic contraction of the musculus orbicularis oculi, is inability of the patient to open the eyes immediately after he has closed them.

ARON, Chicago.

ELEVEN CASES OF OSTEOMYELITIS OF CALCIS. H. VÖLKNER, Beitr. z. klin. Chir. **170**:229, 1939.

Between 1928 and 1938, 11 cases of osteomyelitis of the os calcis were found in the records of the author's hospital. The condition occurs at all ages. The prognosis is very good with conservative surgical treatment, i. e., incision and drainage.

RUBIN, Boston.

TWO CASES OF SACRAL TERATOMA. KARL V. PALLOS, Ztschr. f. Geburtsh. u. Gynäk. **121**:421, 1940.

The histories, gross and histologic pathologic pictures and possible etiologic factors in 2 cases of sacral teratoma are presented.

ADAIR, Chicago.

CONSERVATIVE TREATMENT OF NONSPECIFIC LYMPHADENITIS IN CHILDREN. I. RECHT, Orvosi hetil. **84**:177 (June 29) 1940.

Acute or chronic lymphadenitis was treated with short wave therapy in 93 cases, with good results.

GÖTTCHE, Budapest, Hungary.

OSTEOMYELITIS INFECTIOSA. E. DEUTSCH, Orvosi hetil. **84**:332 (June 29) 1940.

A 14 year old healthy boy had a high fever, and two days later paralysis of the legs developed and he was sent to the hospital with the diagnosis of acute poliomyelitis. The examination in the hospital showed that, besides the paraplegia of the legs, there was anesthesia of the paralyzed region with a zone of hyperesthesia in the region of the eighth and ninth thoracic vertebrae. Then the diagnosis was changed to myelitis transversa. Further observations revealed that osteomyelitis had developed in the eighth and ninth thoracic vertebrae, which probably had caused the myelitis. The postmortem examination confirmed the diagnosis. The cavity of the dorsal canal was filled with pus up to the cervical portion of the spinal column; the leptomeninges were intact. The cause of the transverse myelitis was compression of the spinal marrow by the pus, which originated from the osteomyelitis of the eighth and ninth thoracic vertebras.

GÖTTCHE, Budapest, Hungary.

EIGHT CASES OF LYMPHOGRANULOMATOSIS IN CHILDREN MISINTERPRETED AS TUBERCULOSIS. OVE TAGLKAMP, Nord. med. **5**:107 (Jan. 11) 1940.

Taglkamp briefly reports 8 cases of lymphogranulomatosis in children who were admitted to a hospital as having tuberculosis. Biopsy in each case showed

lymphogranulomatosis. He calls attention to the characteristic roentgen picture of lymphogranulomatous bronchial glands. They are homogeneous, sharply delimited, rounded and situated in the mediastinum or toward the middle of the pulmonary field. There are no perifocal reactions, as in primary pulmonary tuberculosis.

WALLGREN, Göteborg, Sweden.

HEREDITY OF ACHONDROPLASIA. ERNST TRIER MÖRCH, Nord. med. **5**:491 (March 16) 1940.

The author has reexamined a group of Norwegian patients previously reported by Bonnevie as having achondroplasia of recessive heredity origin, and he states that their condition does not correspond to achondroplasia (instead, probably to Morquio's disease). His own observations on Danish and Swedish patients with true achondroplasia show that the disease is always hereditary, is dominantly inherited and that it is produced by mutation with relative frequency.

WALLGREN, Göteborg, Sweden.

PATHOLOGY AND TREATMENT OF EPIPHYSIOLYSIS CAPITIS FEMORIS. N. A. NICOLAYSEN, Nord. med. **6**:733 (April 13) 1940.

The author reports 18 cases of epiphysiolysis capitis femoris. Twelve patients were males, 10 to 20 years of age, and 6 were females, 11 to 21 years of age. Nine were treated with closed reduction and immobilization in the Whitman position, while 9 were treated with more conservative methods. All the patients except 1 were reexamined one and a half to nine years after treatment. The results were judged from subjective symptoms, clinical signs (shortening, muscular atrophy, degree of motility) and roentgenologic observations. There were excellent or very good results in 13 cases, good results in 3 cases and fair results in 2 cases. The group of patients treated by closed reduction showed in every respect better results than the other group.

WALLGREN, Göteborg, Sweden.

CASE OF KLIPPEL-FEIL SYNDROME. JÖRGEN ESCHEN, Ugesk. f. læger **102**:404 (April 18) 1940.

A boy of 13 had been erroneously treated for tuberculous spondylitis. He looked as though he had congenital muscular torticollis and thoracic spondylitis. His neck was short, and there was painless impairment of motility of the neck. Roentgenograms disclosed partial synostosis of several cervical vertebrae and a cervical spina bifida; there were 13 thoracic vertebrae, of which 2 were unilaterally developed and wedge shaped, forming a gibbus. No neurologic signs were elicited. The tuberculin test gave a negative result.

WALLGREN, Göteborg, Sweden.

OXYCEPHALY. B. BROUWER, Nederl. tijdschr. v. geneesk. **84**:501 (Feb. 10) 1940.

In this clinical lecture a survey is given of the disturbances in function of the brain and of cerebral nerves occurring in synostosis cranii. From a practical point of view, the cases of mild oxycephaly deserve special attention, as in these cases causal relations between the complaints and the symptoms of the patient often are overlooked. The polymorphic aspects of the clinical picture of oxycephaly are illustrated by different examples. The methods recommended for operative treatment of this condition are briefly discussed.

VAN CREVELD, Amsterdam, Netherlands.

CEREBRAL RIB AND THE SCALENUS SYNDROME. W. F. SUERMONDT, Nederl. tijdschr. v. geneesk. **84**:2326 (June 22) 1940.

The author describes the symptoms caused by a cervical rib or by abnormal insertion or course of the scalenus muscle. The indications for scalenotomy and for extirpation of a cervical rib are given, and several cases are reviewed.

VAN CREVELD, Amsterdam, Netherlands.

Diseases of the Eye

RETINOGLIOMA IN AN INFANT OF 16 MONTHS. R. ARGAUD and L. CALMETTES, Arch. d'opht. **2**:593 (July) 1938.

The authors describe a case of retinoglioma and present a detailed histologic study with photomicrographs. They express the opinion that it is useless to be too precise as to the type of cell from which the tumor arises. Their researches show that both granular layers can be the sites of origin of the glial tumor. They think that retinogliomas are embryonic neoplasms formed by elements arrested in the development of undifferentiated cells and even of spongioblasts, which instead of differentiating into neoblasts and retinal cells remain in a latent condition, a state of heterotrophic inclusions, inactive for a time but not passing the first year of life without the most capricious hyperplasia and metaplasia to form a malignant tumor. They believe that the generic term retinoglioma completed by the indication of the particular characteristic of each variety, for example retinoglioma with rosettes, is the most convenient of all the designations advocated.

S. B. MARLOW. [ARCH. OPHTH.]

CONGENITAL ANNULAR CATARACT (RINGSTARLINSE-VON SZILY). A. VÁZQUEZ BARRIÉRE, Arch. de oftal. de Buenos Aires **14**:875 (Oct.) 1939.

A case of an annular cataract such as that described by von Szily is reported. A man 34 years of age had congenital nystagmus and had had bilateral cataract since birth. The right eye, operated on when he was 18 years old, showed an upward operative coloboma of the iris occupied by a membranous secondary cataract. The vision was reduced to perception of fingers at 1 meter. There was bilateral horizontal nystagmus of a pendulum type. In the left eye, the vision of which was scarcely perception of fingers at 0.5 cm., the pupil was dilated and irregular and the lens was subluxated upward and inward and was completely opaque and white, with a uniform calcareous aspect. The lens had in its center a circular opening 3 mm. in diameter leading to a tunnel 2 mm. in depth, with irregular excavations into the calcareous substances, the bottom of which was closed by a lead-colored membrane. When this eye was operated on liquefied vitreous immediately exuded and the lens was extracted by means of a Weber loop. After one month vision equaled 0.1. No histologic examination was possible. The author reviews different varieties of cataract described by von Szily. The type under consideration is attributed by the latter to an axial degeneration.

C. E. FINLAY, [ARCH. OPHTH.]

CEREBRAL AND RETINAL ANGIOMA WITH CAPILLARY MALFORMATION IN THE SKIN. C. WESKAMP and I. COTLIER, Arch. de oftal. de Buenos Aires **15**:1 (Jan.) 1940.

The authors distinguish with Lindau, Cushing and Bailey two types of angiomas of the central nervous system: (1) tumors cavernous in structure and of reticuloendothelial origin, which they call hemangioblastomas and which are often accompanied with simultaneous retinal tumors of the same type, constituting the Lagleyze, or von Hippel, disease, and (2) tumors of the cerebrum and other parts of the central nervous system and the skin with the structure of benign angiomas (hemangiomas).

They report a case of a cerebral and cutaneous angioma in which there was a retinal lesions which differed ophthalmoscopically from that of the Lagleyze-von Hippel disease and consisted of dilatation of a retinal vein with numerous arterial miliary aneurysms.

C. E. FINLAY. [ARCH. OPHTH.]

A CASE OF CYST OF THE ORBIT. C. LABORNE TAVARES and P. ELEJALDE, Ophtalmos **1**:24, 1939.

A case of binocular dermoid cyst of the orbit is reported. The extraorbital portion of the tumor had been removed one and a half years previously, but the

intraorbital extension had been overlooked at the time. The mass, which was the size of a nut, was situated in the superior and medial portion of the right orbit, displacing the eyeball 4 mm. downward and 3 mm. outward. The cornea was cylindric in the vertical meridian, and there was myopic astigmatism of 12 D. Vision was 20/30. Microscopic examination of the tumor showed a typical dermoid cyst with a moderate amount of connective tissue surrounding the mass. The literature concerning dermoid cysts of the orbit is briefly reviewed.

The article is illustrated.

P. MONTALVÁN. [ARCH. OPHTH.]

CLINICAL AND HISTOLOGIC OBSERVATIONS IN MELANOSIS BULBI CONGENITA: REPORT OF TEN CASES. H. BRONS, Klin. Monatsbl. f. Augenh. **105**:55 (July) 1940.

Ten patients with melanosis of the eyeball were examined for the purpose of determining a possible relation to a malignant process. The melanosis was discovered at birth in all but 2; it was noticed in one of these one year after birth and in the other at the age of 21. Brons thinks, nevertheless, that a congenital inclination existed in all the patients. Only one eye of each patient was melanotic. The hair and the iris of all except 1 were dark brown. No functional difference existed between the melanotic and the normal eye. The sclera, iris and choroid were involved in every patient, the conjunctiva in 7 and the disk in 1. Symptoms such as asymmetry of the face and telangiectasias of the blood vessels of the face and neck, always on the same side as the melanosis, were observed. One patient had several nevi on the face.

In 1 patient with congenital melanosis a sarcoma of the choroid developed in the melanotic eye. The larger portion of the tumor was unpigmented. A connection between melanosis and sarcoma could not be established in this patient, nor was it possible to prove a transition of melanosis to a malignant process in any of the 10 patients. The author describes several forms of "warty" iris observed. A number of pictures, some of them colored, illustrate the article.

K. L. STOLL. [ARCH. OPHTH.]

FAMILIAL OCCURRENCE OF ATROPHY OF THE OPTIC NERVE AND DEAFNESS. A. SAMUELSON, Nord. med. **6**:769 (April 13) 1940.

Samuelson reports 4 cases (mother and 3 children) of impaired vision depending on atrophy of the optic nerve combined with deafness due to atrophy of the cochlear nerve in a family with 5 children. The anomaly is considered to be due to hereditary or congenital causes.

WALLGREN, Göteborg, Sweden.

Skin Diseases; Allergy

ERYTHEMA NODOSUM FROM SULFANILAMIDE. ADOLPH B. LOVEMAN and FRANK SIMON, J. Allergy **12**:28 (Nov.) 1940.

The authors report a case of erythema nodosum from sulfanilamide. After its first appearance, the eruption was produced twice on further administration of the drug.

The histologic picture was indistinguishable from that of the classic type of erythema nodosum. Chemical tests of tissue taken from an active nodule showed no sulfanilamide.

Patch and intradermal tests with a saturated solution of sulfanilamide on both normal and previously involved areas gave negative results. Patch and intradermal tests with a tissue extract taken from an active nodule and with the blood serum taken at the time of the highest concentration of sulfanilamide in the blood gave negative results on both normal and previously sensitized areas.

MENDELSOHN, New York. [ARCH. DERMAT. & SYPH.]

ASTHMA IN CHILDHOOD: A DISCUSSION OF THE PSYCHOLOGICAL ASPECT. MURIEL BARTON HALL, Brit. M. J. **2**:110 (July 27) 1940.

In this article the author first gives a brief review of the literature according to the increased interest in the medical profession in the association of nervous factors and bronchial asthma. In this article he reports 5 cases in detail.

These cases were chosen "for detailed description, and had the following characteristics in common: (1) Asthma was the principal symptom for which advice was sought. (2) The symptom had been present for at least three years. (3) The patient was incapacitated by the attacks—in one case with respect to ability to follow occupation, in four cases concerning ability to attend school with any regularity, and, in all, as regards ability to enjoy the normal physical and pleasurable activities of childhood."

The treatment in these cases was as follows: "1. Physical examination followed by reassurance of the parents regarding the child's physical state. 2. Advice to the parents on the necessity for allowing the patient freedom to enjoy the normal privileges of childhood, paying special attention to any particularly adverse attitude such as coddling, fussing, over-anxiety, or expecting unduly high standards in lessons or behavior. 3. Independent interviews with the child during which general reassurance was given based on simple explanations of the effects of fear, worry, over-excitement, etc., on the body in general and on the breathing apparatus in particular, and upon the readiness with which these could be overcome. The child was given ample opportunity to speak of his fears and anxieties, and as treatment progressed was encouraged to report personally upon his success in overcoming difficulties at home, at school, in the swimming-pool, or on the sports field. No other form of treatment was employed during the time that the cases were under observation, the use of drugs, even during the asthmatic attacks, being discouraged."

The results of this type of therapy were gratifying. All of the patients improved rather remarkably. There was definite diminution in frequency and severity of the attacks, and an outstanding feature was the effect on the patients' general physique as shown by their ability to take up and retain employment and by their increased capacity for taking part in physical activity or normal excitement without ill effects. There was also a definite improvement in the personality and outlook on life. In the discussion the author strongly urges that more attention be paid to psychogenic influence on asthmatic children.

ROYSTER, University, Va.

ACUTE SYMPTOMS OF INTOLERANCE TO MOTHER'S MILK APPEARING ABRUPTLY DURING FOURTH MONTH. J. CHAPTAL, Bull. Soc. pédiat. de Paris **37**:136 (March) 1939.

A breast-fed infant who was well went into shock during the fourth month of life. It was thought that this might be due to evaporated milk, which he had received for the first time. However, the following day, when he was given about a teaspoon of the mother's milk similar symptoms ensued. No transfer of passive anaphylaxis to a guinea pig was attempted. He was weaned. He was then given cereals and dried milk, which he tolerated well.

BENJAMIN, Montreal, Canada.

THE PROBLEM OF ECZEMA. MARIO SALAZAR MALLEN, Prensa méd. mex. **5**:155 (Sept. 15) 1940.

Eczematous eruptions are divided into two main groups: (1) dermatitides due to sensitivity or allergy and (2) cutaneous reactions without sensitivity. The first group includes the forms of acquired allergy (contact dermatitis, eczematous response to micro-organisms, actinic dermatitis and exudative neurodermatitis) and the forms of sensitivity with hereditary predisposition or atopy, including atopic dermatitis and neurodermatitis circumscripta. The second group includes seborrheic

dermatitis, the cutaneous lesions in diabetes, dermatitis caused by gastrointestinal disturbances and the response of the skin to physical or chemical irritants.

The characteristic symptoms of allergic or atopic dermatitis are first its constitutional character; from 50 to 82 per cent of the patients have a history of allergy in the family, while in healthy children the incidence of familial allergy is only 12 per cent. Treatment modifies the pathologic immunologic response by exclusion of the allergens and sensitivity. For very small children therapy includes watching the diet, control of inhalable allergens and good dermatologic treatment. There is also nonspecific treatment, such as diet rich in acid fats, diet poor in milk and salt (Finkelstein), histaminase (praised by Forman) and dilute hydrochloric acid, which combats alkalosis and prevents somewhat the absorption of allergens.

Dermatitis from contact is rare in children. At times the mango causes dermatitis of the lips and gastrointestinal disturbances, probably from sensitizing the digestive mucous membrane, which reacts with the fruit. Treatment of seborrheic eczema is restriction of fats and carbohydrates and ultraviolet irradiation.

Although the problem of the relation of bronchial asthma and tuberculosis is considered by the experts in asthma as resolved, clinical authorities, such as Jacquelin and Jimenez Diaz, have again insisted on the importance of asthmatic symptoms, as many patients are so affected by a tuberculous allergy. The author undertook this study with profound interest, planning it in the sense of investigating the cutaneous response of asthmatic persons to variable doses of tuberculin. It is known that a positive response to old tuberculin indicates a producer of tuberculin. In the first place he determined the allergic response in healthy persons, or ones without clinical tuberculosis, and then that of persons with known tuberculosis. Of the tuberculous asthmatic persons positive cutaneous reactions were observed in 92 per cent.

The author draws the following conclusions: 1. The theory of tuberculosis in asthma rests on a firm base. 2. Quantitatively the responses to tuberculin are very similar in persons with asthma and without; however, there is a tendency toward a lighter reaction in those with asthma. 3. Quantitatively there exists no greater response of the asthmatic person. 4. The quantitive tuberculin test supports the possibility of a cause and effect relation between tuberculosis and bronchial asthma.

GIFFEN, Toledo, Ohio.

EXPERIMENTAL STUDIES WITH HISTAMINASE OBTAINED FROM THE INTESTINAL MUCOSA. MARIO SALAZAR MALLEN, Prensa méd. mex. **5**:169 (Sept. 15) 1940.

The similarity of the effect in vitro produced by histamine in isolated tissues (muscles), the symptoms of experimental shock (anaphylaxis) and the manifestation of hypersensitivity in man (allergy) has had as a consequence an investigation concerning the physiopathology of this substance and its derivatives.

Histamine is found in tissue extracts and in organs (the liver, gastric mucosa and muscles) as a product of the disintegration of proteins by intestinal flora, in amounts of 10 mg. per kilogram of tissue.

Gadjos, studying another aspect of the problem, stated that in pathologic conditions histamine can work as a drug. Eppinger stated that in certain cases headache and urticaria are caused by the absorption of histamine from the intestines. A fact which should be mentioned in respect to the local effects of histamine is the refractory state of the tissues after primary excitation. The general effects of histamine are arterial dilatation, loss of circulating fluids and reduction of blood volume with a relative increase of the cellular elements.

A quantity of histamine hydrochloride, from 0.005 mg. up to 1 mg., was injected into the external surface of the arm. The result was an intense reaction, the formation of a papule of more than 2 cm. in diameter, with pseudopods and erythema noticeably present. The effects on the individual organs isolated were as follows: activation of the gastric juice, pancreatic secretion and saliva; contraction of the uterus, intestine and arteries, and constriction of the bronchioles. In the isolated heart acceleration of the contractions and reduction of the coronary outflow were observed.

In cases of urticaria, hypersensitivity to cold, angioneurotic edema, dysphagia on eating ice cream and syncope on immersion in cold water, the following phenomena were noted: 1. The typical symptoms could be reproduced by the application of cold. 2. The application of cold to the skin caused a triple response. 3. In three minutes after the application of cold, general symptoms appeared, such as tachycardia, headache, congestion of the face and hypotension. 4. The general symptoms could be retarded at will by ligating above the application of the cold. The triple response of the skin is well known, and the response to the many mechanical stimuli, such as ultraviolet radiation, heat and cold, is probably due to the liberation of substance H (analogue of histaminase).

GIFFEN, Toledo, Ohio.

A CASE OF GENERALIZED FAVUS INFECTION. M. G. REIF, Vestnik ven. i dermat., 1939, nos. 2 and 3, p. 88.

The author reports a case of favus, of six and three years' duration respectively, in 2 sisters, aged 10 and 7 years. In the older girl the scalp alone was affected, while in the other the extremities and the trunk were also involved. Blood cultures showed no organisms. A younger sibling and the parents were free of favus.

BLOOM, New York. [ARCH. DERMAT. & SYPH.]

AN INTERESTING CASE OF ERYTHEMA NODOSUM. H. HALL, Nord. med. **6**:1082 (June 15) 1940.

A boy of 8 years who a year previously had suffered from poliomyelitis with remaining paresis of the right leg, fell ill with fever, erythema nodosum, increased density of the right pulmonary hilus and a positive reaction to tuberculin. The cutaneous eruption was localized solely on the nonparalytic (left) leg. In the author's opinion the eruption was a toxic reaction propagated in a neurogenous way.

WALLGREN, Göteborg, Sweden.

PINK DISEASE. SVEN BRANDT, Ugesk. f. læger **102**:665 (June 20) 1940.

A boy of 2½ years had extreme muscular weakness, anorexia, scaling of the skin on the fingers and toes, tachycardia, hypertonia and leukocytosis. The course was benign, with recovery within two and a half months,

WALLGREN, Göteborg, Sweden.

SOLID CARBON DIOXIDE ROD FOR TREATMENT OF HEMANGIOMAS. G. CREMER, Nederl. tijdschr. v. geneesk. **84**:520 (Feb. 10) 1940.

A large number of hemangiomas were treated with a solid carbon dioxide rod. In general, it can be said that the results were very good in superficial cavernous vascular tumors that were not too large (at most 3 to 4 sq. cm.). The other types are not suitable for this kind of treatment. The technic of the treatment is described.

VAN CREVELD, Amsterdam, Netherlands.

SIGNIFICANCE OF PYEMIDS IN DIAGNOSIS OF SEPTIC PYEMIA. H. W. SCALOGNE, Nederl. tijdschr. v. geneesk. **84**:707 (Feb. 24) 1940.

Scalogne describes metastatic cutaneous lesions accompanying sepsis, known in the literature by the name of pyemids. In the author's case, that of a boy 9 years old, there were, moreover, a meningeal syndrome and thrombosis of the arm. The diagnosis of septic pyemia was made as a result of the finding of pyemids. Both the diagnosis of pyemids and that of septic pyemia were confirmed bacteriologically and by autopsy. The point of issue of the disease was an acute osteomyelitis.

VAN CREVELD, Amsterdam, Netherlands.

SYNDROME OF CUTIS LAXA WITH DEFECTS OF SUPERFICIAL MUSCLES AND EDEMA LYMPHANGIECTATICUM. N. I. HEYBROEK, Nederl. tijdschr. v. geneesk. **84**: 1902 (May 18) 1940.

The author describes an infant with congenital abnormalities consisting of a lax skin (cutis laxa hypoelastica), total absence of the abdominal musculature and of the platysma and edema lymphangiectaticum on both feet. An attempt is made to bring these three abnormalities into one syndrome, with which aim the evidence found in the literature on this point is taken into account. The syndrome can perhaps be explained as a disturbance of fetal development analogous to that described by K. Bonnevie (1934) in the abnormal mouse strain of Bagg and Little. The author is fully aware of the hypothetic character of this explanation.

VAN CREVELD, Amsterdam, Netherlands.

Surgery and Orthopedics

ACCIDENTS IN CHILDREN. MORRIS ZIMMERMAN and SAMUEL ADAMS COHEN, New York State J. Med. **40**:1111 (July 15) 1940.

In the United States 13,500 children died as a result of accidents during 1938. An analysis is made of 752 children under 14 years of age who were admitted to the wards of Gouverneur Hospital, New York, as a result of accidents from 1933 to 1938 inclusive. There were 28 deaths.

Falls were the chief cause of injuries (295 cases). In 15 per cent of the cases there was a history of falling down stairs. The next most frequent cause was automobile traffic (137 cases). Burns were the third most common cause (33 cases). Ten children were admitted for injuries sustained in celebrating the Fourth of July.

AIKMAN, Rochester, N. Y.

PALATOSCHISIS. H. L. M. VAN DER HOFF, Nederl. tijdschr. v. geneesk. **84**:2922 (Aug. 3) 1940.

The author describes in detail his own method of surgical therapy of cleft palate in children without risk of necrosis or fistulas—even in the widest cleft (with illustrations).

VAN CREVELD, Amsterdam, Netherlands.

Miscellaneous

PIERRE GASSENDI AND THE *Elegans de Septo Cordis Pervio Observatio*. G. KASTEN TALLMADGE, Bull. Hist. Med. **7**:429 (May) 1939.

In 1640 a short note dealing with the demonstration of the adult vestige of the foramen ovale was published by Pierre Gassendi in a volume containing gynecologic and embryologic works. This dissection of the heart was done between 1617 and 1622 at Aix by a surgeon, Payanus, who demonstrated a real communication between the left and the right side of the heart. Gassendi directed this publication against Fludd and perhaps also against Descartes. After reproducing the original text and giving a translation, the author presents a careful history of the development of the anatomic knowledge of the heart, considering in particular the question of the perviousness of the septum of the heart. Galen was well acquainted with the fetal foramen ovale and the development of the septum primum; he also knew that the foramen closed at birth, but with him started a theory of invisible pores of the septum, which was not questioned until the early part of the sixteenth century. The persistence of this foramen was not known until Botalli discovered one in an adult in 1565. Severinus Pinaeus declared the adult patent forament ovale an anomaly (1595), and Harvey definitely stated and demonstrated that the septum is impervious.

The "Elegans observatio" was not published for the purposes of demonstrating something new and worth while; he (according to his own words) dug it out of eight year old notes to use it in a controversy. He still maintained, in 1640, "the

outworn and disproved Galenic hypothesis of 'spirits' in the blood of the left ventricle. His error is fundamentally the same as that which Botallus had made twenty-five years earlier, an error . . . which ought never again to have been made after Pinaeus had called attention to it and explained so carefully in 1597 . . ." He still maintained that the septum was pervious, in spite of Harvey's clearly published arguments twelve years before (1628).

There are a scholarly biography and a critical appreciation of the much disputed Pierre Gassendi.

ROBERT ROSENTHAL, M.D., St. Paul.

SULFATHIAZOLE: CLINICAL EVALUATION. WESLEY W. SPINK and ARILD E. HANSEN, J. A. M. A. **115**:840 (Sept. 7) 1940.

The authors summarize the results of the treatment of 128 patients with sulfathiazole, comparing the results with those obtained with sulfanilamide and with sulfapyridine. The effects in pneumococcic pneumonia were as good as with sulfapyridine. Toxic reactions as a rule were less, particularly nausea and vomiting; cutaneous rashes, however, were more frequent. Staphylococcic septicemia and staphylococcic pyelitis were successfully treated.

HEERSMA, Kalamazoo, Mich.

A SIMPLE, EFFECTIVE FABRIC RESTRAINT-SPLINT. MAX KAPLAN, S. O. LEVINSON and PHILIP LEWIN, J. A. M. A. **115**:1098 (Sept. 28) 1940.

The authors describe a cloth restraint for the ankle and wrist which has been modified and augmented to serve several purposes. Coupled with supports it can be used to retain position in cases of poliomyelitis or osteomyelitis, after surgical procedures, etc. The illustrated devices can be made to suit any size or position, and are inexpensive, washable, cleanly and easily applied.

HEERSMA, Kalamazoo, Mich.

THE DIODRAST CLEARANCE AND RENAL BLOOD FLOW IN TOXEMIAS OF PREGNANCY. LEON C. CHESLEY, EMMET J. CONNELL, ELIZABETH R. CHESLEY, J. D. KATZ and C. STEDMAN GLISSEN, J. Clin. Investigation **19**:219 (Jan.) 1940.

In eclampsia, preeclampsia and recurrent toxemia of pregnancy, the renal blood flow, as measured by the diodrast clearance, seems to be characteristically normal. There is a wider range above and below average than in normal subjects. In the few cases of chronic nephritis complicating pregnancy that were studied, the calculated renal blood flow was considerably below the levels found in normal subjects.

GUEST, Cincinnati.

A STUDY OF THE EFFECTS OF SULFANILAMIDE ON ACID-BASE METABOLISM. WILLIAM W. BECKMAN, ELSIE C. ROSSMEISL, R. BARBARA PETTENGILL and WALTER BAUER, J. Clin. Investigation **19**:635 (July) 1940.

Studies were made of changes in the electrolytes of the urine and blood serum of 2 patients before, during and after periods of intensive sulfanilamide therapy; also of the respiratory ventilation, alveolar carbon dioxide tension and exchange of carbon dioxide and oxygen in normal subjects after administration of a single large dose of sulfanilamide and during voluntary hyperpnea. Data thus collected are cited as evidence that the hyperpnea which develops after administration of sulfanilamide should be regarded as an adjustment to an initial removal of fixed base in the urine.

GUEST, Cincinnati.

RESEARCH IN PREVENTIVE MEDICINE: REPORT OF THE LISTER INSTITUTE. Brit. M. J. **2**:122 (July 27) 1940.

This article consists of reports on various studies that have been done by the Lister Institute. The first of these reports is on smallpox vaccination. One hundred and sixty-four subjects were vaccinated for the first time and six weeks later revaccinated by the scarification method. The results afford strong prima facie evidence that in man immunity is not established unless a typical cutaneous vesicle develops.

The therapeutic actions of sulfapyridine and sulfanilamide in the control of experimental infection of mice with Vibrion septique or Clostridium welchii were noted. It was reported that both drugs showed activity but that under these experimental conditions sulfapyridine proved far more effective. It was found, moreover, that when the two drugs were used together a higher survival rate was obtained than when either drug was used independently. They report that when sulfapyridine was given orally it would protect mice against a million lethal doses of meningococci provided the administration of the drug was started immediately after the injection of the test dose; when treatment was delayed for a few hours a much lower degree of protection was obtained. They state also that a combination of sulfapyridine and antimeningococcus serum gives better results than either the drug or the serum alone.

In an attempt to answer the question of whether or not to inoculate people with typhoid vaccine after an outbreak of the disease or when the disease is in occurrence in the vicinity, experiments were carried out in mice. The results showed that inoculation at this time did not cause the disease to be more severe and did not cause the disease to appear in subjects who would not have acquired it. Experiments have been worked out in which diphtheria and whooping cough immunizations have been given at the same time. It was stated that not only does the addition of Haemophilus pertussis vaccine to diphtheria toxoid not interfere with the efficiency of the latter but, on the contrary, the influence of the toxoid is enhanced and guinea pigs receiving the mixture are more highly immunized against diphtheria than those receiving the toxoid alone.

The latter part of this article is a report on some of the vitamin studies; this section does not lend itself to abstracting.

ROYSTER, University, Va.

BIOLOGIC EFFECTS OF THE BATHS OF SALSOMAGGIORE. E. BARENGO, Med. ital. **21**:215 (May) 1940.

The author studied the effect of the baths of Salsomaggiore (Italy) on 8 patients and noted an increase in the hemoglobin value, the red blood cell count and the number of reticulocytes, a slight decrease in the leukocyte count, slight lymphocytosis and monocytosis, increased sedimentation time, a slight decrease in the alkaline reserve and a slight increase in the basal metabolism. There was no change in the blood or urine chlorides and no change in the blood calcium. A slight decrease in the blood uric acid was noted in normal persons, and a slight increase, in persons with arthritis.

MARTOCCIO, Utica, N. Y.

SULFANILAMIDE IN TREATMENT OF CRACKED NIPPLES. HERMANDO MAGLIANO and HECTOR IVAN MANARA, An. Soc. puericult. Buenos Aires **6**:203 (June-Sept.) 1940.

The ideal method of infant feeding would be for each child to nurse from its own mother. Cracked nipples have an important place among the causes for weaning. The pain caused by the suction of the baby is constant and very intense, and infection may develop.

Good results have been obtained with pomades of tannic acid, cod liver oil or resorcinol in clearing the process to cicatrization. Recently the authors have tried a treatment the results of which have surprised them. By the use of sulfanilamide they have been able to cure cracked nipples without discontinuing the baby's breast

feeding. Fifteen case histories are detailed. Two tablets are given each day. The sedation has been early and complete, allowing the infant to nurse. The cracks heal in twelve days. The cure is not followed by a relapse, and with the doses used there have been no toxic effects in a mother or in a child.

GIFFEN, Toledo, Ohio.

NOTOMELIA. W. BLANKE, Beitr. z. klin. Chir. **169**:67, 1939.

A successful operation was performed on a 3 month old infant with a teratoid tumor consisting of rudimentary extremity-like portions found on the lumbar portion of the spine. This is a very rare condition and has been observed only twice before. The patient is still alive after two years.

The name of the condition is derived from the Greek *notos* (back) and *melos* (portion of extremity).

RUBIN, Boston.

PLASMA THERAPY. GÜNTHER SCHALLOCK, Monatschr. f. Kinderh. **83**:307, 1940.

Five children suffering from severe intoxication were treated with large doses of plasma and underwent a pathologic-anatomic examination. They all showed severe lesions due to the injections of plasma. It is presumed that the collapse states observed led to the change of function of the endothelium and thus to the stated morphologic changes. These collapse states may be the expression of anaphylaxis produced by the plasma, but most likely this is a transferred anaphylaxis in the plasma of the donor.

NEURATH, New York.

PLASMA THERAPY. LÖHR, Monatschr. f. Kinderh. **83**:375, 1940.

This is a report on treatment by infusion of plasma given to 56 infants suffering from severe disturbances associated with exsiccation. Only 5 of the children died owing to failure of the therapy. Untoward effects may be avoided by considering contraindications and maybe by improved methods too. By no means will they minimize the main value of plasma as an optimal substituting liquid in cases of acute loss of water.

R. NEURATH, New York.

PLASMA THERAPY. W. UHSE, Monatschr. f. Kinderh. **83**:376, 1940.

There are 133 cases to prove the success of plasma therapy. Of 40 intoxications, 35 were cured; of 12 subintoxications, all were cured. Intoxications, subintoxications and dyspepsia with great loss of water form the indications for this therapy. Severe infections and exudative cutaneous symptoms are not influenced by plasma. After 713 infusions no death occurred that might have been in any way due to the treatment. Only slight undesirable effects were observed, and these were overcome.

NEURATH, New York.

ROENTGEN DIAGNOSIS OF OVER-TERM GESTATION. K. STAMPFEL and E. TSCHERNE, Ztschr. f. Geburtsh. u. Gynäk. **119**:31, 1939.

In a study of 90 term and 22 over-term infants the age was estimated by roentgenograms of the centers of osseous development. A minimal diameter of 7 mm. for the proximal tibial center of growth and 5 mm. for the medial humerus was found only in over-term infants.

POTTER and KASDON, Chicago.

SOCIAL WORKER AT THE CHILDREN'S HOSPITALS IN SWEDEN. CURT GYLLENSWÄRD, Nord. med. **7**:299 (Feb. 17) 1940.

Attention is called to the fact that children's hospitals in Sweden are more and more compelled to admit patients who have no real need of hospital care but who cannot conveniently be treated in their homes because of unsatisfactory social

conditions. Day nursery children need hospital care twice as often as do children in general, and the necessary period of hospitalization is one fourth longer. In order to secure the best possible means of caring for the children in their homes and thus shorten the stay in the hospital and cut down the need of hospitalization, it is recommended that a social worker be associated with each pediatric clinic.

WALLGREN, Göteborg, Sweden.

RESORPTION AND CONCENTRATION OF BLOOD PLASMA AND EXCRETION OF SULFAPYRIDINE. J. MULDER and H. H. VAN DER ZOO DE JONG, Nederl. tijdschr. v. geneesk. **84**:2228 (June 15) 1940.

By a modification of the method of Marshall (van der Zoo de Jong) a series of estimations were made with respect to the resorption, blood plasma concentration, acetylization and excretion of sulfapyridine. The excretion in the urine varied between 65.3 and 87.9 per cent of a single oral dose. Excretion was complete after five to seven days. The concentration in the blood plasma of patients treated orally for several days showed considerable individual fluctuation; in the authors' series with a dose of 6 Gm. in twenty-four hours, the concentration in the plasma was between 2.6 and 13.8 mg. per hundred cubic centimeters. The concentration in the plasma during intramuscular administration likewise varied much individually (with a dose of 6 Gm. in twenty-four hours it was between 2 and 13.6 mg. per hundred cubic centimeters). The rate of acetylization is very variable individually and can be so great as to make the concentration of the free product in the plasma insufficient.

In the cerebrospinal fluid, with oral administration the concentration was 42 to 76 per cent of the concentration of free sulfapyridine in the blood plasma.

VAN CREVELD, Amsterdam, Netherlands.

BUCKY RAY SICKNESS WITH AN UNDULANT COURSE. P. DETHMERS, Nederl. tijdschr. v. geneesk. **84**:2720 (July 20) 1940.

Besides the frequently occurring local reactions to grenz rays with a wavelike course when the dose has surpassed about 500 r, which are described in the literature, hitherto unknown general reactions with a similar course are reported. These reactions manifest themselves in adults by severe headache, great tiredness, dizziness, nausea and sometimes vomiting, the main reaction often accompanied by general malaise and pyrexia; in smaller children they were observed in the form of one day's vomiting or sometimes a diarrhea lasting several days. As these more or less serious general complaints do not differ in any way from the usual signs of roentgen ray sickness and in a few patients examined for this purpose they coincided with rhythmic changes in certain body mechanisms, one may certainly speak of Bucky ray sickness with an undulant course.

VAN CREVELD, Amsterdam, Netherlands.

Society Transactions

CHICAGO PEDIATRIC SOCIETY

JAMES H. WALLACE, M.D., *President, in the Chair*

Regular Meeting, Dec. 16, 1941

Is the Presence of Bile and Food in the Small Intestine Necessary for the Formation of Prothrombin? DR. HEYWORTH N. SANFORD and DR. IRENE SHMIGELSKY.

This paper appears in full in this issue of the AMERICAN JOURNAL OF DISEASES OF CHILDREN, page 894.

DISCUSSION

DR. RALPH KUNSTADTER: I should like to ask whether Dr. Sanford believes, on the basis of this work, that the prothrombin determination is of any value in determining impairment of liver function.

DR. HENRY G. PONCHER: I think there are many clinical experiences not reported in medical literature which would support some of the points Dr. Sanford has made. Patients with congenital biliary obstruction have been observed in whom prothrombin has been maintained at levels above those with which free bleeding occurs, and proved cases of intestinal obstruction have been reported in which there were normal prothrombin values. Tocantins reported a classic case of this type some years ago in the AMERICAN JOURNAL OF DISEASES OF CHILDREN. Such examples, however, do not justify the assumption that vitamin K is made in the liver, as the liver is not a rich source of vitamin K. They merely emphasize the lack of complete information and suggest that physicians should be more critical of the theories current at the present time. There is ample evidence, however, that endogenous sources of vitamin K are probably more important than exogenous supply.

The lack of correlation between maternal diet and incidence of hemorrhagic disease in the newborn and the fact that it is difficult to produce prothrombin deficiency in the human being solely by diet tend to emphasize the importance of bacterial synthesis in the intestine as an important source of vitamin K. It should also be borne in mind that neither food nor the usual intestinal bacteria are necessary for vitamin K synthesis, as Almquist has shown that many air-borne bacteria are more potent in vitamin K than orthodox members of the colon group. Koller's experiment, in which he put an adult on a starvation diet for five days and yet the subject's feces contained 20,000 units of vitamin K per gram, is also significant. In spite of these facts, Dr. Sanford has cited instances in which the pathologic changes in the alimentary tract and the biliary tract might be expected to interfere with absorption of endogenous vitamin K and yet the prothrombin levels remained within normal limits. Similarly, celiac disease or some other condition with steatorrhea, in which absorption of fat-soluble vitamins might be expected to be faulty, seldom has hemorrhage as a prominent symptom. There are undoubtedly many gaps in the knowledge of fat absorption from the bowel and of vitamin K synthesis which is needed to interpret properly the apparent contradictions which Dr. Sanford has cited this evening and those which have been observed by others.

DR. HEYWORTH N. SANFORD: In reply to Dr. Kunstadter's question, I believe that prothrombin estimations as a test for liver function are of doubtful value. It is only with an extreme reduction of liver function that one will begin to find a reduction in prothrombin value. Like other organs of the body, the margin of safety of the liver is so high that only after a massive disturbance will the prothrombin begin to diminish. In the child just described, the prothrombin content as determined by the Quick method did not drop below 65 per cent at any time, yet the hepatic function had decreased at least 70 per cent.

A massive cirrhosis of the liver would cause a reduction in prothrombin, but with this condition other symptoms and signs of diminished function would be of greater value. I do not believe that the ordinary run of slight hepatic disturbances would ever produce any appreciable diminution of prothrombin values.

I have nothing to say regarding Dr. Poncher's discussion except to thank him for his remarks.

Effect of Sulfathiazole in the Treatment of Dysentery in Children. Dr. Eli Rubens and Dr. Max Kaplan.

The value of sulfathiazole (2-[paraaminobenzenesulfonamido]-thiazole) in the treatment of infectious diarrhea was studied at the Cook County Children's Hospital. Forty-six patients were included in this study. They were divided into a group receiving sulfathiazole and a control group, not receiving the drug. Each group was further subdivided into a subgroup whose stool cultures yielded dysentery or salmonella organisms and one with absence of these bacteria in the stools. All the patients received nonspecific therapy, consisting of administration of fluids, of blood transfusion when necessary and of sedatives. The diet was the same for all of them. The duration of the diarrhea after the child's admission to the hospital was used as the criterion of the effect of the drug. Sulfathiazole appeared to have definite value in the treatment of the children whose stool cultures yielded dysentery or salmonella organisms, but was of no statistical significance in the cases in which these organisms were not identified.

DISCUSSION

Dr. Clifford Grulee: I have not much to say specifically on this paper. Things are moving pretty fast these days, and physicians have moved on from sulfanilamide to sulfaguanidine (sulfanilylguanidine). Dr. Lyon, of Huntington, W. Va., has reported some good results with sulfaguanidine in cases of bacillary dysentery, and recently I have had some results with sulfaguanidine which were distinctly illuminating to me.

A child came into the hospital one morning about noon, with a temperature of 102 or 103 F., and since he came from a family that we knew had a history of dysentery we cultured the stools and began treatment with sulfaguanidine. The temperature returned promptly to normal and remained so. The sister, whom we did not see so promptly, because we were not aware of the epidemic, also improved. We have tried it in several cases in which there was no cultural evidence of bacillary dysentery, and in such cases it was not as effective as sulfathiazole; but sulfaguanidine has given better results than anything else in cases of dysentery.

Dr. Noel Shaw: I would like to say a word about some work that Dr. Blatt, Dr. MacFadden and I have been doing at Cook County Hospital with sulfaguanidine in the treatment of infectious diarrhea. The figures are just being compiled. Our experience in some control cases in which we used sulfathiazole compares favorably with the results reported by the essayists. We obtained normal stools in two and nine-tenths days with sulfathiazole; we had a little better results with sulfaguanidine, obtaining normal stools in two and four-tenths days in 35 cases. In other cases in which we used no drugs or perhaps some bismuth prescription, the average number of days in which normal stools were produced was four and six-tenths days. I agree that the diarrheas we have seen recently are not so severe as the type we had some years ago.

Dr. Eli Rubens: I had hoped to be able to report on sulfaguanidine and compare its effects with those of sulfathiazole, but I was unable to do so since the work on sulfaguanidine is still in progress.

Clinical Studies on BCG Vaccination Against Tuberculosis. Dr. S. R. Rosenthal and Dr. E. A. Stack.

Vaccination with BCG as applied by the Tice Laboratories of the City of Chicago Municipal Tuberculosis Sanitarium has been entirely innocuous. This study embraces 833 infants followed for periods up to four and a half years. Prac-

tically all vaccinated children reacted to tuberculin within the first month, and they continued to react, 94.2 per cent doing so at the age of 22 to 27 months and 71.5 per cent at 40 to 45 months. Under the same conditions, of 836 control infants who did not react to tuberculin under 7 months of age, only 10.1 per cent failed to react at the age of 22 to 27 months and only 27.7 per cent at 40 to 45 months.

The time that has elapsed is too short to permit a comment on the efficacy of the vaccine, but it is interesting to note that among the vaccinated children there has not been a single case of tuberculosis, revealed either by clinical or by roentgen examination, notwithstanding the fact that these children live in a highly infected extrafamilial environment, as determined by the high percentage of subjects in the control group who reacted to tuberculin. Among the controls, there have been 7 clinical cases of tuberculosis, with 2 deaths from tuberculous meningitis.

In a review of the whole chapter on the return of virulence of the BCG vaccine in man, it was found that the great tragedy in Germany was most probably due to contaminated vaccine and that the minor disasters in Hungary and Chile, as well as individual cases, were inadequately investigated. When one considers that approximately 3,000,000 infants have been given the vaccine and that there is not yet a single sure case of death from BCG infection, one would indeed be cautious if one doubted the safety of the vaccine for the normal infant.

DISCUSSION

DR. EUGENE A. STACK: You may be interested to know that babies born of tuberculous parents are placed in foster homes by the clinic, and every effort has been made to give them the best possible start in life, in homes which are considered sanitary, with foster mothers who are intelligent and cooperative. This is done whether they are vaccinated or control babies. Also, an endeavor is made to obtain breast milk whenever possible. I think the use of the patch test has aided considerably in popularizing the clinic. A mother will bring a child in for a patch test when she would not bring it in for a test in which the painful procedure of using a needle is involved, especially in view of the fact that the tests are made at least every six months.

DR. J. S. KRUGLICK: It is generally accepted, I believe, that a positive reaction to tuberculin is desirable in a nurse who is in close contact with tuberculosis. At least the number of tuberculous infections that develop in a positively reacting group of nurses under such circumstances is shown to be fewer than the number developing in a negatively reacting group, and it may even be advisable that an infant going into a tuberculous home should have a positive reaction; this can be believed in a benign fashion, but there is something more to be said than appears on the surface.

If it is assumed that the question to be answered is whether or not infants should be vaccinated with BCG, then the answer in a great measure depends on the infant's home circumstances and environment. It would be most desirable, of course, to go through life without ever having contact with tuberculosis, and fortunately the number of positive reactions to tuberculin in any given group of school children is rapidly decreasing. At the present time, high school children rarely have an incidence of positive reactions of over 25 per cent.

Dr. Mayer has said that tuberculosis develops in 30 per cent of all persons who give positive reactions to tuberculin. Personally I think this proportion is high; but in the analogy which I am going to make the percentage is irrelevant to the reasoning.

The vaccination is done in the arm, and a positive reaction is thus produced with an avirulent organism, one which is incapable of reproduction. Should, then, a subsequent infection occur in the normal manner, it would be an exogenous infection type of tuberculosis. In other words, in the vaccinated group one can do away with the endogenous reinfection tuberculosis. But there is even more to be said.

Let us take 1,000 children who have positive reactions as a result of vaccination, and another 1,000 who have positive reactions produced by the ordinary method of infection. Let us grant that under comparable conditions there will be one-half as much tuberculosis in the vaccinated group as in the other group. If, however, 50 per cent of the children infected by the regular channels go through life without contracting tuberculosis, the number of cases in the two groups will still be the same. If less than 50 per cent of the group of 1,000 infected by the ordinary method receive the infection, then there will be fewer cases in this group than in the 1,000 vaccinated. It would seem, then, that whether or not a child should be vaccinated depends to a large extent on the expectancy of a positive reaction to tuberculin for that child.

While an exactly correct guess cannot be made in each case from the type of home, environment and circumstances, one should, within a limited area, be able to tell whether a child falls into the group for whom vaccination is desirable or into a group who stand a better than average chance of not contracting tuberculosis at all.

I should say that Dr. Rosenthal's work with BCG is the finest study that has been made along this line, and within a short period the work itself will answer many of the questions raised today.

DR. E. T. MCEMERY: I want to compliment the essayist on the work he has done. It has entailed a tremendous amount of study. It is only in an organization like a tuberculosis sanatorium that one can carry on work of this type. It is research in which one cannot get results in a short time, but when it is reviewed, say in ten years, the value will be apparent.

DR. THOMAS P. SALTIEL: I should like to ask whether the BCG vaccine was used by mouth. I believe Calmette mentioned that at one time early in the experimental stage this was done.

DR. RALPH SPAETH: If I understood correctly, Dr. Stack stated that the children are removed from the tuberculous environment either before or soon after vaccination with BCG. This procedure would make it difficult to determine whether the immunization or the breaking of contact with tuberculosis is responsible for preventing occurrence of the disease.

At the Children's Service of the Chicago Relief Administration, children are removed from immediate contact with tuberculous parents or siblings. Under such an arrangement, the later incidence of tuberculosis, as indicated by change of the Mantoux reaction from negative to positive, is very negligible. The material used for the Mantoux test is obtained from the Chicago Tuberculosis Institute. It is a special intermediate strength of purified protein derivative. Incidentally, all children with positive Mantoux reactions have roentgenograms taken periodically, especially at the onset of puberty. Mantoux tests, if the reactions are negative, are repeated at least every two years.

DR. EUGENE A. STACK: The contact babies are placed in foster homes for six or eight weeks, until the reaction to tuberculin becomes positive. However, for children from the control group the treatment is the same.

DR. S. R. ROSENTHAL: If I understand Dr. Kruglick correctly, he bases his analysis on the premise that of children who react to tuberculin a definite percentage will acquire tuberculosis, because their altered state makes them more susceptible to the disease. This is far from being the case. The results of Myers and of Friedman and Billings bear this out. The former has noted that 15.02 per cent of his positively reacting children contracted tuberculosis over a twelve year period when no separation of the children was effected; Friedman and Billings reported an incidence of tuberculosis of only 1.3 per cent when removal from the original environment and supervision were instigated. The development of tuberculosis is primarily dependent on the degree of exposure to the tubercle bacillus, and not on a positive reaction to tuberculin.

I agree with Dr. Kruglick that vaccination will have its greatest benefits in groups that are most exposed to the disease.

I wish to thank Dr. McEnery for his kindness toward the work presented. It will take many more years before the full value of the study will materialize. However, I may add that in numerous ten to fifteen year studies reported by French, Rumanian and South American workers, the results have been gratifying.

In answer to Dr. Spaeth, removal of the child is for only six to eight weeks in cases of closed tuberculosis. After this time the child is returned to its tuberculous environment. Recent work has shown that the method of ascertaining the infectiousness of a person solely by smears of the sputum is fallacious. Yet the law requires only such an examination.

JAMES H. WALLACE, M.D., *President, in the Chair*

Regular Meeting, Jan. 20, 1942

The Measurement of Children's Abilities. DR. MILTON A. SAFFIR (Psychologist, Bureau of Child Study, Chicago Public Schools; Psychologist, Psychological Service Center).

The measurement of human abilities, one of the specialized functions which psychologists perform, has had widespread and varied application. Mental tests are used in schools, colleges, hospitals, guidance clinics, courts, social agencies, the army and navy, industries and many other institutions. In medicine, particularly psychiatry and pediatrics, the technics of psychologic measurement contribute valuable aid to diagnosis and treatment.

In cases of suspected mental retardation it is often easy to make gross errors unless psychometric technics have been employed. Knowledge of the exact degree of defect is important in arriving at decisions concerning placement, school enrolment and management. If genuine mental retardation is established, much harm is done by encouraging unwarranted hopes for "outgrowing" the condition. On the other hand, many children thought to be retarded or even defective actually have normal intelligence or better. They suffer from reading or other disabilities which after diagnosis through specialized psychologic tests can be treated successfully. Children with school problems are often referred to the pediatrician. Measures of their abilities are essential in management of such children. Even if the pediatrician's contact is indirect, his influence on parents makes it desirable for him to understand the child's test results and their implications.

In cases of neurologic disorders, glandular dysfunctions, behavior and personality problems, nervousness and speech disturbances, mental measures may be very valuable for diagnosis and treatment. In routine supervision of healthy children it would seem as worth while for the physician to record mental growth through periodic tests to observe the physical growth.

The technics of mental measurement involve: (1) selecting from among the several thousand tests available those which are appropriate to the nature of the problem and the child; (2) securing the appropriate attitudes on the part of the child; (3) administering the tests and scoring the results under rigorously controlled conditions; (4) exploring and evaluating possible invalidating circumstances, and (5) interpreting the results of the tests in the light of the problem presented. In addition to intelligence tests, among which the most widely used in clinical work is the revised Stanford-Binet, there are available tests to measure and diagnose achievements, special aptitudes, reading and other disabilities, personality, interests and vocational guidance possibilities. Examiners need a thorough background of training in psychology and a suitable personality, as well as experience and skill in psychometric technics.

Test results are reported, generally, as a percentile rank, a grade score, an age equivalent or a quotient. For intelligence tests, the mental age represents the mental capacity at a given time, while the intelligence quotient (I. Q.) represents the rate of mental growth. The intelligence quotient is the ratio of mental to

chronologic age multiplied by 100. In Illinois institutions intelligence quotients are interpreted as follows: 0 to 39, idiot; 20 to 44, imbecile; 45 to 69, high grade mental defective; 70 to 79, borderline defective; 80 to 89, dull; 90 to 109, average; 110 to 119, superior; 120 to 139, very superior; over 140, extremely superior.

Children with mental ages below 5 years or intelligence quotients below 50 do not usually profit from public school attendance, and those with intelligence quotients below 80 may profit most from ungraded classes.

The advantages of using psychologic measurement technics in studying a child's abilities include: (1) greater precision; (2) relative freedom of the examiner from bias or other individual characteristics; (3) relative avoidance of confusion of mental abilities with other abilities or with extraneous factors, such as personality, appearance, physical handicaps, special training, talents or disabilities, and (4) comparability of results of tests made at different times or by different examiners.

A vast amount of published research supports the conclusion that a child's intelligence quotient remains relatively constant, except under unusual circumstances. The probable error of measurements is calculable, and is not high. The validity of psychologic measurement, when properly administered and interpreted, is an accepted scientific fact.

Behavior in Organic Disease. DR. DOUGLAS BUCHANAN.

Management of Mentally Handicapped Children. DR. BERT I. BEVERLY.

A mentally handicapped child is one whose growth and development deviate from the average to such a degree that he fails to make an adjustment in his home, in a public or private educational institution and/or in society.

It is now generally recognized that educable mentally handicapped children should be reared in their homes rather than in state institutions. State institutions are for uneducable children and for those who come to present uncontrollable behavior problems.

While there is a relationship between mental deficiency and delinquency and dependency, the cause is primarily emotional rather than intellectual. Mentally handicapped children do not have the environmental advantages of normal children and therefore have emotional difficulties more frequently.

Mentally retarded persons can have mental health as well as can persons with normal intelligence.

Mental health is based on children's having security in their parents and being allowed to grow up according to their own individual patterns. They then form habits of self reliance which give them confidence in their ability to face difficult situations.

It is generally accepted that mentally handicapped children require especially trained teachers and special facilities in the school systems.

This paper will be published in full in the *Journal of the Illinois State Medical Society.*

DISCUSSION ON PAPERS BY DR. SAFFIR AND DR. BEVERLY

DR. MARGARET W. GERARD: I am pleased to hear from Dr. Beverly how far these programs for the mentally defective have gone; physicians have waited twenty years for this. It is true that the problem has always been more a social than a psychiatric one.

I think it is particularly interesting for those who are concerned with functional diseases to have a clear explanation of integrated action of behavior, integrated development and disintegrated behavior reactions resulting from emotional disturbance. Functional diseases also are associated with disturbance of the nervous system. If one can think of these diseases as the result of disintegration of physiologic function, one can explain them in functional or physiologic terms. This perhaps brings the two separate disciplines psychiatry and neurology closer together, and helps one to recognize that something functional is not necessarily esoteric but is related as much to the functioning of the nervous system as is anatomic injury.

I should like to elaborate on the value of mental tests. Dr. Saffir gave the impression that mental tests may be used to measure accurately the ability of the child. It is true that frequently one does use the intelligence quotient as a measure of absolute intelligence. However, emotional factors enter into the reactions of a child when he is taking a test and lead to a distorted view of his true capacity. On the other hand, I think Dr. Saffir does not give adequate credit to the mental tests as aids in evaluating mental problems. The tests are used often to evaluate the amount of interference which emotional problems cause in intellectual activity. It is interesting that in this particular field one can plot the progress of treatment according to the change in the intelligence quotient. The child may start with an intelligence quotient of 70 and a wide scatter, and after treatment, when he is symptom free and emotionally well adjusted, the intelligence quotient may be 110 to 115 with a stable level. Thus one is able to use mental tests as an indication of the effect of treatment on a particular phase of a child's behavior.

DR. GEORGE J. MOHR: I want to express my gratification at what Dr. Beverly said with respect to the program for retarded children. In clinical practice it seems that, no matter what social or economic level one is dealing with, the practical problem of the mentally handicapped is disappointing from the standpoint of the pediatrician, the child and the parents. The programs now contemplated will give great aid and comfort to all and certainly will lead to better handling of the child.

Dr. Saffir has made a most useful statement on mental tests. A word as to some practical experience in the use of mental tests and their value in clinical application. The other day the parents of a 7 year old boy became greatly disturbed because he is to be excluded from school. They have the impression that he is seriously retarded, and, by virtue of the child's behavior, there is evidence that he is so. The psychologist is able to show that, far from being mentally retarded, he has an intelligence quotient of 110, which is ample for him to function well at his grade level. However, one finds that he is immature and infantile, as a result of being handled by rather elderly parents and an elderly nurse, who have made it unnecessary for him to meet actively the life situations usually met by children of his age. He stands out in distinct contrast with other children, makes no progress in school and has just begun to read. In addition, the psychologist demonstrates that this boy suffers a special reading disability; i. e., he evidences in marked degree the tendency to reversals referred to by Dr. Saffir. This in itself makes it difficult for him to learn to read by ordinary methods and, added to his already described personality handicaps, puts him in a position in which he cannot profit by exposure to the ordinary classroom situation. This child is able to make good progress when these important details are made clear through the help of the psychologist. Institution of proper handling in the first grade avoids common reactions to failure. These consist of anxiety reactions, destruction of self confidence and diminution in the ability of a child to perform at a level consistent with his innate intelligence and capacities. Much reconstructive work is necessary with such children.

DR. MILTON A. SAFFIR: I appreciate Dr. Gerard's calling to attention the fact that mental tests are useful not only in evaluating intelligence but in providing standardized situations whereby one can obtain insight into the emotional forces activating the child. I think one must be careful to keep these aspects distinct from the mental measurement aspects. I recognize that in given instances a wide scatter may be indicative of emotional instability, but I feel it is very easy to make mistakes. It used to be thought that wide scatter always indicated emotional instability. It is known now that this is not so, although in some instances it may well be that the emotional problem affects the pattern of test successes.

I believe the program for improved facilities for the educable mentally handicapped is a splendid one, and the psychologic profession is as much interested as the medical profession. There is now in existence in the Chicago public school system a complex program of adapting the setup within the schools to the individual needs of the children. In addition to the varied special schools and classes,

there is, through the adjustment teacher service, provision for individual tutoring, individualized materials and other specialized facilities. Thus a child may sit in a seventh grade room and use third or tenth grade materials if his needs so dictate. This provides the means not only to diagnose the child's needs but actually to meet them.

SOCIETY FOR PEDIATRIC RESEARCH

L. Emmett Holt Jr., M.D., *President*

A. A. Weech, M.D., *Secretary*

Annual Meeting, Skytop, Pa., April 26-27, 1939

First Session

Wednesday Afternoon, April 26

Equilibrium of the Diabetic Child. Dr. J. D. Boyd and Dr. R. L. Jackson, Iowa City.

Since diabetes mellitus is not curable, the ideal of management should be the approximation of normal conditions as far as possible. This implies, among other measures, the maintenance of normal blood sugar levels and the avoidance of glycosuria, even of mild degree. Though less stringent treatment may seem to meet the patient's needs, the physician should not be content with poor control if a more advantageous status can be attained. Fourteen years' experience with therapy directed toward physiologic levels of control has established the harmfulness of continuous or intermittent glycosuria, even of mild degree, and has demonstrated that continuous aglycosuria not only is desirable but is attainable for the average diabetic child under suitable management.

Once the patient has achieved normal blood sugar levels and has been maintained in that state for several weeks, he loses much of the variation in response which has been considered typical of the diabetic child. The dosage of insulin necessary to maintain the desired control becomes constant for a given quantity of food and degree of exercise, and fluctuations of blood sugar are fairly normal. With shorter periods of preliminary control, the patient does not become truly stable, tending to oscillate between glycosuria and shock. The daily insulin requirement is much higher during this stage of incomplete stability than it is after true stabilization has been established. The well controlled patient remains stable under careful home management for months at a time under a constant regimen of exercise and diet, without requiring alteration of dosage of insulin.

When the well regulated patient is used as a subject for the study of the efficacy of protamine zinc insulin or crystalline zinc insulin as compared with amorphous insulin, no reduction of the requisite dosage is evident. Moreover, crystalline zinc insulin differs in no respect in its qualitative effect as compared with amorphous insulin of equal unitage.

Protamine zinc insulin offered no advantage over the other two forms except in cases of mild involvement, requiring only small doses of insulin. When the twenty-four hour requirement did not exceed 20 units, or 1 unit per kilogram, some patients could maintain equilibrium with a single dose in twenty-four hours. In general, it proved difficult to maintain predictable levels of blood sugar when protamine zinc insulin was used; the level of control tended to be decidedly inferior to that with amorphous insulin. Since these disadvantages outweighed any questionable advantage, the use of protamine zinc insulin has not been continued.

It is concluded that physiologic levels of control are feasible and desirable and that when patients so controlled are treated with the newer forms of insulin they fail to demonstrate the superior response which has been attributed by some observers to the protamine and crystalline zinc products.

Disturbances in the Electrolyte Metabolism in a Case of Severe Acrodynia. Dr. J. A. Anderson, Minneapolis.

The discovery of unusually low values for the potassium and sodium ions in the serum of a patient who had acrodynia with severe hypertension (blood pressure 166 systolic and 126 diastolic) prompted an extensive investigation of the electrolyte metabolism in this patient. Complete studies on mineral balance were made under the following experimental conditions: low mineral diet; restoration of the serum electrolytes by intravenous administration of lactate-Ringer (Hartmann's) solution; oral administration of potassium chloride; oral administration of potassium chloride and intramuscular administration of extract of adrenal cortex; intramuscular administration of the extract alone; oral dosage with sodium chloride and intramuscular dosage with the extract.

The following observations were made: 1. The low mineral diet produced further decrease in the serum electrolyte values, accompanied by severe aggravation of all symptoms and an increase in blood pressure to 192 systolic and 136 diastolic. 2. Complete restoration of the serum electrolytes, with the exception of potassium, by the intravenous route was without clinical effect. 3. The oral administration of potassium chloride produced retention of potassium chloride and water but failed to influence the blood pressure or the clinical symptoms. 4. When potassium chloride was given orally and extract of adrenal cortex intramuscularly, there was a retention of potassium within the tissues without increase in the intracellular water. This was accompanied by a dramatic fall in blood pressure and striking clinical improvement. 5. The administration of the extract alone produced further clinical improvement, with return of the blood pressure to normal (96 systolic and 58 diastolic). 6. When sodium chloride and the extract were given, a marked increase in water retention occurred, which failed to disturb the improvement previously obtained.

It is suggested that the restoration of potassium within the body may have been the chief cause of the striking fall in blood pressure and the disappearance of symptoms, through the effect of the potassium ion on the activity of the autonomic nervous system.

Studies in Experimental Anaphylaxis: The Influence of Electrolyte and Water Changes in the Body on Anaphylaxis. Dr. M. I. Rubin, Dr. M. Rapoport and Miss Elizabeth Dudley, Philadelphia.

In a previous study it was demonstrated that dehydration of guinea pigs produced a marked reduction in their susceptibility to experimental anaphylactic shock. Since there are also losses of salt from the animal body during dehydration, the experiments to be described were made in a study of the relative roles of loss of water and loss of salt in this protective action. A group of 25 male guinea pigs weighing 250 cc. each were used as controls. They were passively sensitized to horse serum, with a dose that resulted in the death of 22 of the animals. A group of 20 animals given the same dose of sensitizing serum were depleted of sodium chloride by the technic of Darrow and Yannet, which allows withdrawal of body salt without loss of body water, before the injection of the shocking dose of horse serum. Only 4 of the 20 animals died—a highly significant reduction in mortality, comparable to that obtained with animals dehydrated by restriction of water.

In a second experiment it was demonstrated that rendering a guinea pig edematous exaggerated the anaphylactic response. As contrasted to a control group of 20 guinea pigs receiving a dose of serum which resulted in the death of but a single animal, a group of 20 guinea pigs rendered edematous by subcutaneous or intraperitoneal injection of a physiologic solution of sodium chloride had 7 deaths—a significant increase in mortality. An increase in susceptibility to anaphylaxis was produced by increasing the sodium chloride content of the animal without altering its water content (intraperitoneal injection of a 1.8 per cent solution of sodium chloride, as described by Darrow and Yannet). Only 1 of the 24 control animals in this experiment died, while 6 of the 24 experimental animals died.

These experiments indicate that alterations of the body concentration of sodium chloride (interstitial fluids) influence the anaphylactic response. In the experiment in which a physiologic solution of sodium chloride was given, presumably there was alteration not in the concentration of sodium chloride, but in the total amount of body fluid with its normal amount of sodium chloride. This experiment suggests that the water concentration of the body also influences the anaphylactic response.

In our experiments, situations which increase the interstitial fluids exaggerated the anaphylactic response, and situations which decrease the interstitial fluids decreased this response.

In another experiment intravenous injection of small amounts of an isotonic solution of potassium chloride decreased markedly the anaphylactic response (the amount of potassium chloride solution given, 0.75 cc., was too small to influence the blood sodium).

Adrenal Insufficiency in an Infant. DR. A. M. BUTLER and DR. R. A. ROSS, Boston.

A 17 month old infant had shown poor gain in weight, increased pigmentation in the skin and a mild infection of the respiratory tract throughout his life. With the addition of a mixture of sodium chloride and sodium bicarbonate to his food or by the administration of potent extract of adrenal cortex, the patient could be maintained in reasonably good health. Withdrawal of these specific remedies led consistently to a crisis suggesting Addison's disease. Associated with the crises were found high concentrations of serum potassium and nonprotein nitrogen and low levels of serum chloride and sodium. There was difficulty in making a definite diagnosis. It is suggested that the infant presented an example of adrenal insufficiency.

A Case of Sexual Precocity Associated with Adrenal Insufficiency. DR. L. WILKINS and DR. W. FLEISCHMANN, Baltimore.

A 3½ year old boy was one of two children born of normal parents. The other child was apparently a female pseudohermaphrodite. Almost from birth the patient showed signs of rapidly advancing development of the male sexual apparatus. At 3½ years the child's external genitalia and secondary sexual characteristics resembled those of an adult, and body growth and osseous development were advanced far beyond the levels normal for his age; mental development was defective. From an early age the boy had a remarkable craving for salt, which he had been permitted to gratify. On admission to the hospital he was not given unusual amounts of salt, and after a week he suddenly died. At the time of death the blood showed a low sodium content and a high nonprotein nitrogen value characteristic of adrenal insufficiency. Autopsy disclosed: (1) diffuse hyperplasia of the androgenic zone of the adrenals with almost complete absence of the other elements of the cortex; (2) diffuse hyperplasia in the testes, with apparently the same type of cell noted in the adrenals, with absence of the seminiferous tubules and of other testicular structures; (3) hypertrophy of the accessory sexual apparatus—the penis, prostate and seminal vesicles—and the presence of pubic hair and adolescent laryngeal changes, and (4) pituitary basophilism but no changes in the other endocrine glands or in the brain.

The essential lesion in this case is believed to be hyperplasia of the androgenic zone of the adrenal occurring in embryonic life and persisting postnatally. The hyperplasia of the androgenic zone caused destruction of the "interrenal" elements of the adrenal cortex and led to corticoadrenal insufficiency. Although in a few cases of female pseudohermaphroditism recorded in the literature there have been symptoms suggestive of adrenal insufficiency, this is the first patient proved to have died of adrenal failure. The case supports the theory that the androgenic zone has a function entirely different from that of the portions of the cortex which control the electrolyte balance. The presence of the adrenal cells in the testes is explained by the fact that the adrenals and the gonads arise from the same area in the sexual ridge of the embryo, so that the adrenal cells could

readily be included in the developing testes. The condition is regarded as the analogue in the male of pseudohermaphroditism occurring in the female, both being due to early embryonic hyperplasia of the androgenic zone of the adrenals. About 40 cases of female pseudohermaphroditism due to diffuse adrenal hyperplasia have been reported, but until now no case of macrogenitosomia in the male has been proved to be due to hyperplasia. On the other hand, in 12 instances, tumors of the androgenic zone in boys have caused symptoms identical with those in our case. The cause of embryonic adrenal hyperplasia is not known. The pituitary is probably not responsible, as it develops later in embryonic life. There is probably a strong hereditary factor, as in 8 families the condition has occurred more than once in the same generation. In no instance, however, has either parent shown any evidence of sexual or other endocrine abnormality.

Thyrotoxicosis in Children. Dr. W. A. Reilly, San Francisco.

A ten year study was made of 62 patients with definite thyrotoxicosis, who were followed two to twenty-five years. The natural history of the disease and the etiologic factors, including the influence of the pituitary gland, were considered. Many of the patients came from the mountains of California, where iodine deficiency is common. When it originates in childhood this disease characteristically leads to excessive skeletal growth and retardation maturity.

A comparison was made of medical, roentgen and surgical therapy. For 30 patients medical treatment was started. This consisted of rest in bed, sedation and a high caloric diet; in half of the group the disease was arrested after an average of ten months' therapy, as judged by a seven year follow-up study. These patients were less toxic than the half of the group not successfully handled by a medical regimen. Doses of 1 to 5 drops daily of compound solution of iodine U. S. P. were as effective as 10 to 15 drops. The larger doses were reserved for the occasions when they would be most helpful and most needed, i. e., during a crisis or before operation.

Roentgen therapy was successfully used in 5 cases, as judged by a five year follow-up study. Treatment with 150 units was repeated daily for six days. After a month's rest such a course was given again. Occasionally a third course was necessary. It is felt that roentgen therapy will accomplish considerably more in the future. In the past doses have been too small, and treatment has been repeated too infrequently.

Thirty-three patients were operated on, with removal of 90 per cent of the gland in one procedure. This therapy arrested the disease in over 90 per cent of the cases, as judged by a six year follow-up study. In childhood it is necessary to remove a large part of the gland in order that this result may be accomplished. The operation did not lead to infantilism. There was a recurrence in 10 per cent of the cases in which operation was performed. As there was recurrence in 25 per cent of the entire group of 62 patients, it is felt that in this group surgical treatment has been the most successful form of therapy. Recurrences were noted three to twelve years after the last evidence of toxicity. Hypothyrodism occurred 6 times after surgical intervention, and once it spontaneously resulted from the disease. It was permanent in 2 patients who had had surgical operations. The symptoms were mild and readily controllable.

Hypoparathyroidism occurred 4 times after surgical therapy. In 2 cases it was permanent but mild. The disease in childhood seems to have produced little effect in adult life; occasionally adults were extremely tall owing to the effect on growth.

Orientation of Specificity in Nucleoprotein Antigen Monofilms at Air-Water Interfaces. Dr. L. A. Chambers, Philadelphia.

A surface agglutinogen released from hemolytic streptococci (group A) by sonic disintegration was shown by Mudd and his collaborators to possess both group-specific and type-specific reactive sites when in solution; when in situ at the bacterial surface the type specificity predominates. It is therefore probable

that the architecture of the surface layer plays a role in determining the specific reactivity of the organism.

The extracted agglutinogen, a nucleoprotein, spreads readily on the surface of water or of a dilute buffer solution. Monomolecular films so formed may be transferred by the method of Blodgett to glass slides coated with ferric stearate. By suitable dipping procedures it is possible to secure two types of film surface, one with the air face (*AB*) exposed and one with the reverse orientation (*A*). When included as reactants in ordinary agglutination mixtures, such preparations have been found to possess at least some of the reactive properties of the bacterial surface. When they are cosensitized with homologous organisms by combination with homologous antiserums, adsorption of bacterial cells occurs. The amount of sensitization may be estimated by a count of the adsorbed cells per unit area of film surface.

Through use of the slide agglutination technic it has been found that the agglutinogen remains serologically active when spread at an air-water interface and that the two faces of the film possess different specific reactive properties. The results indicate that the *AB* film is predominantly type specific, while with the *A* film group-specific reactive sites or sites of even broader specificity predominate.

Furthermore, there is suggestive, though inconclusive, evidence that the nucleic acid component of the agglutinogen complex is at the air face (*AB* film) and may contribute the type specificity.

The Vitamin C Index: A Measure of the Vitamin C Stores. Dr. L. Kajdi, Dr. J. Light and Mrs. Charlotte Kajdi, Baltimore.

The aim of the present study was to establish the suitability of a parenteral tolerance test based on one or two plasma determinations for estimating the vitamin C nutrition in infants. Blood was drawn while the subject was fasting or after ingestion of a meal free from vitamin C. Then 200 mg. of ascorbic acid was injected intramuscularly. Four hours later a second sample was drawn. The vitamin C content of the plasma was estimated according to the method of Ingalls.

Seventy tests were performed on 44 children, who were divided into five groups: Group 1 included patients with manifest clinical evidences of scurvy. Group 2 was made up of scorbutic patients who had been given a single intramuscular injection of 200 mg. of ascorbic acid. Group 3 comprised patients with histories suggestive of deficiency but without definite symptoms of scurvy. Group 4 embraced scorbutic patients who had had multiple treatments. Group 5 was composed of miscellaneous patients hospitalized for other conditions.

Our results indicate that the vitamin C level in the plasma during fasting is not an adequate criterion for diagnosis in the individual case. Although the group averages are significantly different, the individual values overlap; some values for group 5 are just as low as those for group 1. The concentration of vitamin C in the plasma four hours after injection of the test dose is a much more satisfactory criterion. This single determination gave correct information in 91 per cent of the cases. Even sharper differentiation is obtained when both the initial and the final concentration of vitamin C in the plasma are considered. The "vitamin C index" refers to the product of the initial value of the plasma vitamin C and the increase in value four hours after injection, multiplied by 100. For our series the index was always below 0.8 for patients with active scurvy. For groups 2 and 3 it was between 0.9 and 6. For groups 4 and 5 it was above 6 with 2 exceptions; one patient had pneumonia and empyema and the other a severe streptococcic infection. For normal persons and for fully treated scorbutic patients the index was usually above 30. In other words, in 97 per cent of the cases the index was a satisfactory criterion for the recognition of scurvy and severe deficiency.

If a patient was treated daily, both the fasting values and the index showed regular increases; but if the treatment was interrupted for several days, the fasting values were unpredictable while the four hour values and the index showed

the regular progressive increases. The rate of recovery of stores was variable in different patients, regardless of complicating infections.

No correlation was found between the severity of the changes revealed by the roentgen rays and the clinical and chemical findings; indeed, indexes in some of the cases in which roentgen findings were negative were just as low as in cases in which the roentgen findings were typical. This discrepancy is explained on the grounds that the deficiency must be in operation for considerable time before changes recognizable roentgenologically will develop and that the presence of rickets may complicate the roentgen picture. The chemical test is a measure of the immediate scorbutic state, while the changes seen on roentgen examination are an indication of its duration.

Effect of Vitamin K Concentrate on Prothrombin Time and Clotting Time in the Newly Born, with Special Reference to Unnatural Bleeding. Dr. W. W. Waddell Jr. and Dr. D. Guerry III, Charlottesville, Va.

The prothrombin clotting time as calculated by the Quick method and the clotting time as revealed by the capillary method were determined at varying intervals for 10 newly born infants to whom vitamin K concentrate (1 cc. after twenty-four hours and 0.5 cc. on each of the two following days) was administered orally. The resultant curves were compared with similar curves for 10 newly born infants who did not receive the concentrate. In the control series the prothrombin time was found to vary from subject to subject and from day to day in the same subject, while the infants treated with vitamin K were found to maintain a low prothrombin time, which was well within the normal adult range. The clotting time as determined by the capillary method was found to follow closely the prothrombin time. Prothrombin times in the control series were found to be highest on the second and the third day and to approach normal levels at the end of the sixth or seventh day. In 2 cases high prothrombin times and clotting times were reduced dramatically within a short period (two to three hours). In 1 of these cases abnormal bleeding from a wound in the heel which was continuous for about twenty-four hours ceased entirely half an hour after the administration of the concentrate. Therapeutic application of these findings as a possible method of preventing hemorrhagic disease of the newly born as well as hemorrhage from birth injuries is suggested. The approach by oral administration of the concentrate to pregnant mothers is also suggested. We are now engaged in work with this objective in mind; our findings will be reported later.

Creatinuria of Premature Infants. Dr. S. Z. Levine and Miss Eleanor Marples, New York.

The creatine (and creatinine) excretion in the urine of 20 premature infants given human milk or cow's milk was determined for a total of two hundred and seventy-eight days.

When subjects were given human milk, with an average daily nitrogen intake of 391 mg. per kilogram, the average creatine coefficient (milligrams of creatine nitrogen per kilogram per twenty-four hours) was 0.36, the range being from 0 to 1.3 mg. of nitrogen. When subjects were taking cow's milk, with an average daily intake of 832 mg. of nitrogen per kilogram, the average creatine coefficient was 1.08, with a range of 0.07 to 3.40 mg. of nitrogen. With comparable nitrogen intake, the creatine coefficient of full term infants averaged 3.16, with a range of 0.67 to 4.16 mg. of nitrogen. The average figures for creatine represented 8, 18 and 39 per cent of the total urinary creatinine excretion, respectively, for the three groups of infants.

The administration of aminoacetic acid, creatine or thyroxin in amounts which invariably produced a prompt and significant rise in the creatine excretion of full term infants did not induce a similar response in premature infants who had not been excreting creatine previously.

An explanation for the diminution in creatinuria of premature infants is not at hand, but the evidence suggests that it may be related to the rapid velocity of growth in these subjects and to the concomitant deposition of muscular tissue, which demand more creatine for storage and utilization within the body than is available from the precursors of the diets customarily given.

Effect of Sleep on Regulation of Body Temperature in Infants and Children. DR. R. L. DAY, New York.

The loss of weight (insensible perspiration), the rectal temperature and the cutaneous temperature of the extremities were measured during sleep. Over 200 observations were made on 14 subjects between the ages of 6 months and 3½ years. The functions mentioned were found to go through a series of changes during the onset and course of sleep. The rectal temperature showed a consistent fall, which amounted to about 0.95 degree F.; the amount of the fall was not affected by environmental temperatures between 72 and 84 F. The rate of loss of weight (which was measured continuously) was, however, influenced by the environment. The onset of sleep, especially in warm and humid conditions, was frequently marked by a temporary increase in rate of weight loss, which sometimes amounted to over 100 per cent. It seems that in conditions in which loss of heat is difficult the body makes an especial effort to lose heat and that as a result the fall in rectal temperature proceeds, unaffected by the environmental temperatures (between 72 and 84 F.). After the initial increase, the rate of weight loss decreases, becoming constant when the rectal temperature does.

The rectal temperature becomes constant suddenly, and the moment when this occurs is marked by some slight movement on the part of the patient. This suggests a regulatory process. Such regulation is further suggested by the fact that the fall in temperature would be greater than it is if the fall in heat production in sleep (as reported by Levine and others) were the sole physiologic change. Additional evidence that regulatory processes guide the thermal changes in sleep was obtained: There is a marked dip in the rate of weight loss at the moment that the rectal temperature becomes level when the rate of weight loss is artificially increased by radiant heat directed on the subject.

The following tentative theory may explain all these facts: The fall in rectal temperature in sleep may be caused not solely by decreased heat production, but, as is the case in the recovery from fever, it may be guided by the heat regulatory center.

Second Session

Wednesday Evening, April 26

Use of Sulfapyridine in the Treatment of Pneumonia in Infants and Children. DR. J. P. SCOTT, Philadelphia.

Of 100 patients with pneumonia, 54 were treated with sulfapyridine, the 46 who were given expectant treatment being used as controls. In no case was serum used; but transfusions and oxygen therapy were given freely to both groups. All blood cultures were negative.

Sulfapyridine was given in powdered form in small amounts of fruit juice in six equal doses given daily at four hour intervals for four days only, in a calculated dose of 1.5 grains (0.09 Gm.) per pound (0.5 Kg.) of body weight per day. No bicarbonate of soda was given, and there was no increase in the initial dose.

Blood counts were done on the treated patients on admission to the hospital and every two days thereafter. In a single case there was a significant fall in hemoglobin content and erythrocyte count, which were partly restored when administration of the drug was stopped and were further restored when transfusions were given. In the cases of 7 of the treated patients large decreases of granulocytes were noticed; in 2 cases, the extent of the fall occasioned some

anxiety, although restoration was prompt after cessation of the drug. In no case of this series was hematuria noted, but it has occurred in other cases in which this drug was used in the same hospital. No other urinary changes were observed. Vomiting was the principal untoward symptom presented by practically all patients, but it often abated after a few doses. In 2 cases it was severe enough to warrant withdrawal of the drug. It was fairly severe in 5 cases, moderate in 8 cases and trifling or absent in 39 cases.

The value for free sulfapyridine in the serum was estimated in 10 cases after two days of therapy. It varied from 1.2 to 12 mg. per hundred cubic centimeters and was not correlated with the clinical effect.

None of the sulfapyridine-treated patients died. The drug usually had a serum-like effect in precipitating a fall of temperature in twelve to twenty-four hours; a permanently normal temperature was attained within an average of one and nine-tenths days from the beginning of treatment. In the control cases the average duration of fever was four and five-tenths days. That the cases were comparable in regard to severity of involvement is shown by the fact that the treated patients were sick on an average of two and ninety-three hundredths days before treatment and the control patients two and eighty-five hundredths days. Two patients in the control group died, one of pertussis complicated by pneumonia and the other of pneumonia complicated by meningitis (both of type XIV). Empyema did not occur in either group.

I feel that sulfapyridine has a valuable effect in shortening the course of pneumonia and in rapidly detoxifying the patients and that with careful supervision toxic effects are not common. I believe that the arbitrary dose chosen could be reduced without decrease in the effectiveness of the drug.

Sulfapyridine in the Treatment of Pneumonia in Infants and Children.
Dr. R. L. J. Kennedy, Rochester, Minn.

From Dec. 1, 1938, to April 1, 1939, 33 infants and children entered the hospital service of the Section on Pediatrics of the Mayo Clinic suffering from lobar pneumonia, bronchopneumonia and capillary bronchitis. Treatment with sulfapyridine was begun immediately on their admission. At first, the dose employed was 0.5 grain (0.03 Gm.) per pound (0.5 Kg.) of body weight per twenty-four hours. This was increased later to 0.75 grain (0.49 Gm.) and finally to 1 grain (0.06 Gm.) per pound. This dose is smaller than that which has been employed by others.

The concentration of the free drug in the blood ranged from 2 to 10 mg. per hundred cubic centimeters. Pneumococci from the sputum were typed in only 3 of 20 instances. Hemolytic streptococci were recovered from the pharynxes of only 2 of 14 patients. The duration of illness before sulfapyridine therapy in 30 cases in which no major complications occurred was one day for 13 patients, two days for 7 patients, three days for 5 patients, four days for 3 patients and five days for 2 patients. Regardless of the duration of the illness previous to administration of the drug, the temperature began to decrease in most instances soon after the first dose was administered. A definite downward trend was noted within twelve hours in the temperatures of 23 patients, within twenty-four hours in those of 4 patients and within thirty-six hours in those of 3 patients. The clinical improvement paralleled the decrease in temperature.

The question of whether the downward trend of temperature can be ascribed to the drug cannot be answered with certainty. The effective concentration in the blood and the time required to obtain this concentration have not been determined; unless it is proved that the effective concentration can be obtained within four to six hours, it cannot be maintained that the decrease in the temperature of these patients was caused by the drug. Seven of the 23 patients whose temperature began to decrease so promptly had been ill for three to five days. However, temperatures of many patients having pneumonia have been seen to decrease between the third and the fifth day of illness when no supposedly specific treatment had been administered, so that in the 7 instances just cited the results of therapy cannot be considered remarkable.

Except for vomiting, toxic effects were not noted. Vomiting was suffered by about a third of the patients, but administration of the drug was not discontinued on account of it. Prolonged delirium after the temperature became normal was observed in a single patient; it disappeared promptly when the drug therapy was discontinued. Cyanosis which may have been caused by the drug was noted in 1 patient. No effect on the leukocyte count was observed. Complications in the group of 33 patients consisted of otitis media in 7 instances, acute hemorrhagic nephritis in 1 instance, furunculosis in 1 instance and empyema in 2 instances; 1 patient who died had a congenital anomaly of the heart.

It was concluded that the results in this series of patients justify further trial of sulfapyridine in the treatment of pneumonia in infants and children and that there is need for information regarding the optimal dose, the optimal concentration in the blood and the toxic effects which may be produced by the drug.

Use of Sulfapyridine Against Primary Pneumococcic Pneumonia in Infants and Children. Dr. W. C. Stifler Jr., Baltimore.

There have been 43 cases of primary pneumococcic pneumonia treated with sulfapyridine in the Harriet Lane Home. In each instance, definite homogeneous pulmonary consolidation was demonstrated roentgenographically and pneumococci which were identified by type-specific serums were obtained from the nasopharynx.

The sulfapyridine was given at six hour intervals; the total twenty-four dose varied between 1.2 and 6 Gm. In some instances the entire twenty-four hour dose was given on admission. Administration of the drug was continued for five to seven days after the temperature had become normal and for a longer period when otitis media, infection of pleural fluid or thickening of the pleura was present and when pneumococci were persistently found in the nasopharynx. The concentration of free sulfapyridine in the blood was determined in each case. These levels varied widely, ranging from 2.0 to 15 mg. per hundred cubic centimeters. Recently my co-workers and I have begun to administer the drug with an equal quantity of sodium bicarbonate. Dr. Hodes will discuss a possible reason for this.

The results in this series of cases are similar to those reported by others. The temperature usually became normal within twenty-four to forty-eight hours after administration of the drug was started. The temperature dropped similarly in all cases without regard to the type of pneumococcus or to the duration of the pneumonia before the beginning of therapy. There were no deaths. The patients with pneumonia which we have seen during the present season have been perhaps not quite so severely ill as those seen during the past few years. There were only 4 patients in the series whose blood cultures yielded pneumococci. Most of the patients were clinically improved as soon as the temperature became normal. We believe that sulfapyridine shortens the period during which the patient appears to be severely ill, but we do not believe that the fall in temperature is indicative of a natural crisis.

Sulfapyridine sometimes produces toxic effects. Anorexia, nausea and vomiting were seen frequently but were never sufficiently severe to necessitate stopping the drug. One patient who developed granulocytopenia recovered soon after drug therapy was discontinued. We have encountered no cases of severe hemolytic anemia. Four patients had hematuria; in each instance the blood had entirely disappeared from the urine within a day after sulfapyridine treatment was stopped. Dr. Hodes will discuss a possible mechanism of the hematuria. Mild cyanosis was seen twice, and a morbiliform rash, which disappeared in twenty-four hours, was seen once.

Use of Sulfapyridine in Treatment of Pneumonia Associated with Measles. Dr. H. L. Hodes and Dr. R. G. Shirley, Baltimore.

Since the mortality rate of primary pneumonia in young children is comparatively low, the effect of a given form of therapy may be difficult to evaluate when a small group of patients is studied. On the other hand, the prognosis for

pneumonia associated with measles is much less favorable; the mortality rate under these circumstances may reach 25 per cent in children under 3 years of age.

The present report deals with the use of sulfapyridine in the treatment of 47 patients with measles and pneumonia. Thirty-seven of the children were under 3 years of age. All the patients were shown to have pneumonia by roentgen examination. Pneumococci, which were typed, were isolated from the nasopharynx in each case. In addition large numbers of beta hemolytic streptococci (group A, Lancefield) were cultured in material from the throats of 11 of the 47 patients. Pneumococci were obtained on blood culture three times, and Haemophilus influenzae was isolated once.

In all but 6 patients the temperature became normal within thirty-six hours after the beginning of sulfapyridine therapy. Clinical improvement usually paralleled the fall in temperature. All the patients recovered; in none of them did empyema develop. Sulfapyridine, however, did not strikingly influence the resolution of the pulmonic infiltration.

It was demonstrated that pneumococci persisted in the nasopharynx during and after administration of sulfapyridine. This was regarded as evidence that sulfapyridine does not cause improvement in the patient with pneumonia by completely destroying the pneumococci present.

The toxic effects of the drug which were noted were nausea, vomiting, mild and temporary neutropenia and hematuria. The last-mentioned condition was seen in 2 cases; both patients recovered promptly when the drug was withdrawn. The probable cause of the hematuria was shown to be the formation of small calculi. These calculi, which were made up chiefly of crystals of acetylsulfapyridine, appeared to have produced hematuria by mechanical injury to the kidney pelves and to the ureters.

Treatment of Pneumonia with Sulfapyridine. DR. R. WARD, Philadelphia.

Sixty-two patients with pneumonia were treated with sulfapyridine. Twenty-five patients had typical pneumococcic lobar pneumonia; 8 had atypical pneumococcic pneumonia, usually characterized by the prominence of dyspnea, by signs of bronchiolitis and bronchitis and by roentgen evidence of patch consolidation; 14 had pneumonia caused by various organisms other than the pneumococcus. Attempts were made to isolate the causative organism in the sputum, in material from the nose, throat and nasopharynx and in the tracheobronchial secretions. There was a fair correlation between the types of pneumococci in the nasopharynx and those in tracheobronchial secretions.

In 37 cases the temperature dropped permanently to a normal level within forty-eight hours of the start of drug therapy and in 10 cases within five days. Of the remaining 15 patients, 7 had empyema; of these, 5 with pneumococcic and 1 with staphylococcic infection showed no response, while 1 with streptococcic involvement was without infection after forty-eight hours of treatment. Three infants had no appreciable fever, although 2 were critically ill. Five deaths were attributable to bronchiolitis and interstitial pneumonia, which in 1 case was caused by the hemolytic streptococcus, type 19. All these deaths occurred in children less than 2 years old. Four died within twenty-four hours of first receiving the drug. One patient with a congenital malformation of the heart died after eighty hours. One death, clearly caused by sulfapyridine, occurred in the group of 37 cases in which the temperature responded promptly. The patient was a 4 year old girl who contracted pneumococcic pneumonia in the ward; granulocytopenia appeared on the seventeenth day of treatment. She died ten days later with complete aplasia of the bone marrow.

An initial dose of sulfapyridine was given in amounts varying from ½ to 1 grain (0.03 to 0.06 Gm.) per pound (0.5 Kg.) of body weight. Half this dose was given immediately and the remainder in two hours. An equivalent amount was given in four or six divided doses every twenty-four hours for an average of six days after the permanent drop in temperature. In most cases the level of free sulfapyridine in the blood after twenty-four or forty-eight hours was between 3 and 9 mg. per hundred cubic centimeters. In the experience of my associates

and myself there was no direct correlation between the level in the blood and the size of the dose. Vomiting, with few exceptions, did not appreciably affect the level in the blood. Almost all the children more than 2 years old vomited, whereas only half those less than 2 vomited. The first dose was vomited rarely, the second dose a little more frequently and the maintenance doses most frequently. This suggests that a large initial dose may be the best means of obtaininng quickly an effective level in the blood.

In our series, except for the single instance of bone marrow aplasia described, evidence of serious toxicity was absent. In 1 patient methemoglobinemia developed and cyanosis was marked; otherwise cyanosis was insignificant. Anorexia and vomiting, although common, were rarely serious. Paraesthesias and urticaria appeared in 1 case each. No urinary abnormalities were observed.

Third Session

Thursday Morning, April 27

Production and Use of Hyperimmune Whooping Cough Serum. Dr. A. C. McGuinness, Dr. W. A. Bradford and Miss Janet G. Armstrong, Philadelphia.

Hyperimmune human whooping cough serum was produced by the following method: Donors who have had whooping cough in childhood are given three 8 cc. courses of phase I whooping cough vaccine containing 10,000,000,000 organisms per cubic centimeters at four month intervals; blood for serum is taken one month after the third course of vaccine. Serum produced in this manner possesses a high opsonocytophagic index as well as an agglutination titer which varies from 1:1,280 to 1:5,120, values far in excess of those usually found in convalescent serum.

Of 83 infants and children given injections of this serum after exposure to whooping cough, 65, or 78.3 per cent, failed to contract the disease. Of the 18 who contracted whooping cough, 11 neither whooped nor vomited. These children were given from 10 to 20 cc. of serum, and the dose was usually repeated in five to seven days because of the long incubation period of the disease.

Of 100 infants and children treated with hyperimmune serum after the onset of the disease, the course of the disease was checked or considerably modified in 63, apparently somewhat modified in 20 and not affected in 17. Included in this group of 100 subjects were 51 infants 6 months of age or younger. There were 3 deaths in the treated group. Those who died were all white children 2 months of age; all had bronchopneumonia at the time serum was first administered. In 1 case the serum was first given four days before death, in 1 case thirty-six hours before death and in the third case twenty-four hours before death. The general plan of treatment was to give 10 to 20 cc. of serum every other day for three or four doses.

Results of a Search for Poliomyelitis Virus in Stools of Patients with Various Diseases. Dr. A. J. Vignec, Dr. J. R. Paul and Dr. J. D. Trask, New Haven, Conn.

Previous experience had shown that the poliomyelitis virus could be recovered from specimens of stool inoculated intracerebrally. The experimental mortality with this route, however, has been excessive. Accordingly, in 1937 attempts were made to isolate the virus by intraperitoneal inoculation. They proved successful, and the experimental mortality was reduced from an average of 61.1 per cent for the intracerebral route to 11.3 per cent for the intraperitoneal route. Because of this the intraperitoneal route was used almost exclusively in the present series of experiments.

Since it was not essential to concentrate the inoculum into the small quantities necessary for intracerebral inoculation, a simple method for preparing specimens of stool could be utilized. Of the three methods which had previously proved successful, the use of aqueous stool extracts, without further treatment, seemed

most practical. Stools were emulsified in 100 to 150 cc. of sterile distilled water, and the emulsion was allowed to settle in the refrigerator for about six hours. The supernatant fluid was then withdrawn, and 15 per cent ether was added to it as a bactericide. This material was kept in the refrigerator overnight, and the following day it was centrifuged at 1,000 revolutions per minute for twenty minutes. The middle layer of fluid, which was relatively clear, served as the inoculum.

The customary criteria for a positive result were adhered to, viz: (1) the production of clinical experimental poliomyelitis; (2) the demonstration of typical histologic lesions in the cords of affected animals, and (3) passage to another monkey.

Because of the low incidence of poliomyelitis in this country during the past year, but few specimens of stool from patients with clinical poliomyelitis could be obtained. However, through Dr. C. A. Andrewes and Dr. J. S. Ranson a number of specimens were mailed from England. These were prepared in England in the manner described, with the exception of centrifugation, and were mailed on the day of collection and preparation. The average time spent in the mails was twelve to seventeen days.

Twenty-one specimens of stool from patients with poliomyelitis in England, 3 specimens from patients in the United States and 16 specimens from controls in the New Haven Hospital were examined. The control specimens were obtained from patients suffering from diseases other than poliomyelitis. Fifty-five experiments were performed with these specimens.

The poliomyelitis virus was recovered in 2 instances from specimens mailed in England. The patients who yielded the virus were without residual paralysis. One of the positive specimens was collected on the seventh day after onset and inoculated sixteen days later; the other was collected on the eighteenth day after onset and inoculated thirty-four days later. Negative results attended the reexamination of these stools and of specimens collected on the one hundred and twenty-seventh and on the seventy-fourth day, respectively.

The simple method described of preparing specimens of stool combined with intraperitoneal inoculation has proved innocuous to monkeys. The 2 positive results confirm previous findings as to the prolonged infectivity of human stools and the extraordinary stability of the virus in this type of medium.

Occurrence of Antibodies Against Equine Encephalomyelitis in Human Serums. Dr. F. H. Wright, New York.

The cause of some forms of acute primary encephalitis is now known. There are two ways in which the laboratory may aid in diagnosis: (1) isolation and identification of the virus from brain tissue and (2) detection of specific neutralizing antibodies in convalescent serums.

An eastern and a western strain of equine encephalomyelitis virus are encountered in the United States. Although in regard to infectivity for animals they are similar, their immunologic reactions and geographic distributions are distinct. Antibodies of high titer against the western strain of the virus were found in the blood of 8 persons in Minnesota who were convalescing from acute encephalitis. Similar high titers against the eastern strain of the virus were found in the blood of 5 of 9 patients during the Boston epidemic last summer. Significant titers apparently appear in the blood six to ten days after the onset of symptoms. The preliminary data collected indicate that the neutralization test is a reliable method of demonstrating a previous infection with equine encephalomyelitis.

Amino Acid Composition of the Protein of Cow's Milk and of Human Milk. Dr. S. S. Bernstein, Mr. E. F. Beach and Miss Olive Hoffman, Detroit.

A fundamental consideration in determining the nutritive value of proteins is their content of various amino acids. We have prepared two protein fractions from samples of cow's milk and human milk: casein, by isoelectric precipitation, and soluble protein, by precipitation from the whey with trichloroacetic acid at a concentration of 8 per cent. These fractions were analyzed for basic amino

acids by the Block method, for tyrosine and tryptophan by the method of Folin and Marenzi, for cystine by the method of Graff, Maculla and Graff and for methionine by the method of Baernstein. The distribution of total nitrogen between casein, whey proteins and nonprotein nitrogen was determined for the various samples of milk.

The cow's milk used contained 494 mg. of protein nitrogen per hundred cubic centimeters, of which 405 mg. was casein and 89 mg. whey protein nitrogen. The human milk contained 126 mg. of protein nitrogen per hundred cubic centimeters, of which 49 mg. was casein and 77 mg. whey protein. The percentage distribution of these amino acids in the casein proteins of cow's and of human milk, respectively, was 1.8 and 1.5 per cent histidine, 3.3 and 2.8 per cent arginine, 5.8 and 4.4 per cent lysine, 6.0 and 5.2 per cent tyrosine, 1.1 and 1.0 per cent tryptophan, 0.1 and 0.5 per cent cystine and 3.2 and 2.2 per cent methionine. Similarly, the percentages of histidine were 0.8 and 0.9, of arginine 3.1 and 3.7, of lysine 6.9 and 4.6, of tyrosine 3.8 and 4.4, of tryptophan 1.3 and 1.4, of cystine 2.2 and 2.4 and of methionine 2.7 and 1.9 for cow's and for human milk whey, respectively.

The quantities in milligrams of each of these amino acids in 100 cc. of cow's and of human milk were calculated, and the specimens were found to contain, respectively, 55.5 and 10.5 mg. of histidine, 113.1 and 31.3 mg. of arginine, 207.1 and 42.4 mg. of lysine, 192.2 and 44.0 mg. of tyrosine, 39.2 and 11.4 mg. of tryptophan, 17.8 and 15.9 mg. of cystine and 106.5 and 18.7 mg. of methionine. The cow's milk contained four to five times as much of each of the amino acids except cystine, which was about equal in both types of milk. For better comparisons of the two kinds of milk, the amino acid content of cow's milk if diluted to the same protein nitrogen content as that of human milk was calculated; it would contain, per hundred cubic centimeters, 14.1 mg. of histidine, 28.8 mg. of arginine, 52.7 mg. of lysine, 48.9 mg. of tyrosine, 10.0 mg. of tryptophan, 4.5 mg. of cystine and 27.1 mg. of methionine.

There is a marked similarity in the amino acid content of human milk and that of cow's milk, nitrogen for nitrogen. The chief differences are in the cystine and methionine. The totals of these two sulfur-containing amino acids are similar in the two varieties of milk, but in diluted cow's milk the cystine level is lower and the methionine level correspondingly higher than in human milk.

Utilization of Intravenously Administered Amino Acids by Young Children with the Nephrotic Syndrome. Dr. L. E. Farr, New York.

The failure of children with the nephrotic syndrome to regenerate plasma protein when fed a diet approximately optimal for nitrogen assimilation cannot be explained solely on the basis of loss of protein in the urine. Further, the rapid regeneration of plasma protein during recovery is, within wide limits, independent of the protein content of the diet.

Recently Farr and MacFadyen discovered a disturbance of amino acid regulation in children with the nephrotic syndrome. This disorder was characterized by a chronic deficit of plasma amino acid, which gradually disappeared before complete recovery. In addition to this continuing deficit of plasma amino acid, there were occasional periods of critical fall in the plasma amino acid level accompanied by severe constitutional manifestations. Recovery to precritical levels usually took place within forty-eight hours. In view of this disturbance of amino acid physiology, it seemed likely that if intravenously administered amino acids were utilized they might, besides furnishing material for regeneration of protein, further stimulate the mechanism regulating the level of plasma proteins to a more nearly normal condition.

Four children, 2 of each sex, who were receiving a constant nitrogen intake were followed with studies on nitrogen balance over a period of months, each analytic period being one week. At suitable intervals amino acids derived from a casein hydrolysate (furnished by Mead Johnson and Co.) were given intravenously. The results indicated that the amino acid preparation was a suitable source of nutritional nitrogen. Although occasionally the increase in the positive nitrogen balance was greater than the amount of nitrogen given intravenously,

usually there was no effect on the nitrogen balance. A preexisting negative nitrogen balance could not be made positive under the conditions of study. No consistent effect on the level of the plasma albumin was noted.

Nitrogen Balance During Enteral and Parenteral Administration of the Amino Acids of Hydrolyzed Casein. Dr. A. T. Shohl, Dr. A. M. Butler and Dr. K. D. Blackfan, Boston.

A metabolic study was made on 6 infants weighing from 4 to 7 Kg. who were given a food which contained 20 per cent amino acids from the enzymatic hydrolysis of casein as the sole source of nitrogen, plus 18 per cent olive oil, 56 per cent carbohydrate and 5 per cent minerals, with additions of vitamins A, B, C, D and G. The experiment included eight control periods with diets of milk mixtures and ten periods with amino acid food. Specimens of urine were collected for four days and of feces for three days during each period. The nitrogen metabolism was measured by the percentage of nitrogen in the feces, by total urinary nitrogen and by the percentages of urea, ammonium and amino acid excretion in the urine. The amounts of the various nitrogen fractions excreted and of the positive nitrogen balances were approximately the same for the infants when they were fed the amino acid food as when fed the usual milk mixtures.

Amino acids obtained by the enzymatic hydrolysis of casein were given intravenously, a 1.5 to 5 per cent solution with 10 per cent dextrose plus 0.45 per cent sodium chloride being administered continuously for twenty-four hours to 5 patients, with a total of 9 different observations. These studies were made on 4 of the infants previously mentioned and on a child in the terminal stages of tuberculous meningitis. There were five febrile reactions, three of which were so severe that the administration was discontinued. One infant had convulsions, 1 local twitching of one arm and 1 a transient rash.

When amino acids were introduced intravenously the urine contained about twice the amount of amino acids and a larger amount of undetermined nitrogen than was usual in the periods when amino acid food or a cow's milk mixture was ingested. Six balance studies were made on 5 patients. The child with meningitis showed nitrogen equilibrium. One infant, who received an insufficient amount, was in negative nitrogen balance. Positive balances were found for 3 infants, in 1 of them on two different occasions. The amounts of nitrogen retained were similar whether the infants received the amino acids orally or intravenously.

Obstructive Loculated Pulmonary Emphysema Simulating Abscess of Lung in Lobar Pneumonia: Roentgen Observations. Dr. J. P. Caffey, New York.

A roentgen study was made of a series of children with pneumonia. Changes typical of abscess of the lung were visualized in all cases (large areas of diminished density with or without fluid-air levels). The clnical course of the disease was not affected by these lesions. The lesions themselves involuted completely without residual clinical or roentgen manifestations. The benign course and the complete recovery suggested that probably little actual pulmonary necrosis had occurred. The most likely explanation of the formation of these abscess-like lesions is that they are produced by obstructive emphysema behind check valve bronchial obstruction, which permits entrance of air into this segment of the lung but prevents its egress, thereby causing localized dilation and rupture of the alveoli and formation of large pulmonary bullae and blebs. The fluid present is the inflammatory exudate from the alveolitis of lobar pneumonia. The fluid disappears as the pneumonia clears.

There were 2 cases of localized obstructive emphysema following tonsillectomy and simulating a large abscess of the lung.

There was a single case of multiple massive obstructive emphysema simulating congenital cysts of the lung.

Lipodystrophy: Report of a Case, with Metabolic Studies. Dr. J. S. Harris and Dr. R. Reiser, Durham, N. C.

Lipodystrophy of the cephalothoracic type was observed in a 9 year old boy. The disease began at the age of 6 years and reached full evolution in three years, without affecting the general health of the patient. Metabolic studies were made and the results compared with those of similar studies on 2 normal children of the same age. The patient showed normal digestion and absorption of fats, as determined by analyses of stool. However, after a meal of fat the oxidation of fats was delayed and much less intense than in the controls. The total lipoids of the blood serum reached a maximum six and one-half hours after the meal, in contrast to the smaller maximum four hours after in the controls. In addition, there was a slow but marked rise in the phospholipid content and to a lesser extent in the esterified cholesterol fractions. The dextrose tolerance tests showed a low tolerance to the ingestion of both 1 and 2 Gm. of dextrose per kilogram of body weight. The total creatinine coefficient and the proportions of creatine in the urine were abnormally high.

It was concluded that in this patient there was an abnormality in general metabolism in addition to any local disturbances, which might or might not be present, in the tissues affected by the lipodystrophic process.

Factors Affecting Retention of Nitrogen and Calcium in Period of Growth: Effect of Thyroid on Calcium Retention. Dr. J. A. Johnston and Dr. J. W. Maroney, Detroit.

This paper has been published in full (Am. J. Dis. Child. **58**:1186 [Dec.] 1939).

Metabolic Studies in a Case of Resistant Rickets (DeToni-Fanconi Type). Dr. I. F. Gittleman and Dr. J. B. Pincus, Brooklyn.

The patient came under our observation three years ago, at the age of 4½ years. Her symptoms at that time were inability to walk, marked anorexia and failure to grow. Physical examination showed an undersized but fairly well nourished child. The epiphyses of the long bones were enlarged. The liver was felt 2 inches (5 cm.) below the right costal margin, and the spleen also was enlarged. There was no anemia. The blood pressure was normal. The urine was acid in reaction and contained acetone and a small amount of albumin. Sugar (which was made up equally of levulose and dextrose) was present in concentrations up to about 0.5 per cent. Tests indicated that renal function was normal. No malformations were demonstrable in the genitourinary system. The blood serum contained 11.4 mg. of calcium, 2.3 mg. of phosphorus, 120 to 350 mg. of cholesterol, 23 mg. of nonprotein nitrogen and 11 mg. of urea per hundred cubic centimeters. The plasma carbon dioxide varied from 28 to 53 volumes per cent. The concentration of serum protein was 7.4 Gm. per hundred cubic centimeters; the ratio of albumin to globulin was normal. There was 33.7 Bodansky units of phosphatase in the serum. Roentgen study showed widening and fraying of the epiphyses of the long bones, indistinct centers of ossification and marked osteoporosis.

Mineral metabolic studies revealed that the calcium and the phosphorus balance were negative but rapidly became positive when vitamin D therapy was instituted. In spite of this improvement in the absorption of calcium and phosphorus from the intestinal tract, the phosphorus concentration in the blood remained low, and no evidence of orderly healing could be noted in the roentgenograms of the long bones. Vitamin D was administered in amounts as high as 3,000,000 units over a period of several weeks without effect on the phosphorus level in the blood. We were also unable to raise the bicarbonate concentration in the blood stream to normal levels by the administration of a buffered mixture of citric acid and sodium citrate or of disodium acid phosphate. Sugar tolerance curves like those of diabetes and respiratory quotients as low as 0.76 showed that the child was unable to burn fat properly. The administration of insulin failed to influence the

values favorably, but the administration of lipocaic after ten months produced a normal sugar curve, reduced the ketone bodies in the blood, caused a disappearance of the ketone bodies in the urine, reduced the total lipids in the blood and raised the carbon dioxide from 28 to 44 volumes per cent. Tests indicated that hepatic function was normal. The administration of thyroid failed to induce healing of the rachitic process. There was no evidence of any increased secretion of parathyroid hormone or of any disturbance referable to the anterior lobe of the pituitary.

The rickets in this patient can be classified as belonging to the DeToni-Fanconi type. A disturbance of fat metabolism appears to have resulted in ketosis, which in turn so interfered with the mechanism for concentrating phosphorus in the blood that orderly calcification was prevented. The favorable effect of lipocaic suggests that the primary dysfunction resided in some of the internal secretions of the pancreas.

Refractory Rickets in Identical Twins. Dr. D. J. McCune, New York.

Twin sisters were recognized to have rickets at 18 months of age. Irregular treatment with cod liver oil and viosterol combined with generous exposure to sunlight during the summer failed to produce healing. At 3½ years both sisters required osteotomy for correction of bowed legs; the deformity of the lower extremities recurred rapidly after operation.

At 9 years one child was bow legged and the other knock kneed. In all other respects the physical features were highly similar: Both children were dwarfed; the palpable epiphyses were moderately enlarged. Roentgen examination confirmed the presence of active rickets of moderate severity. In both cases the serum calcium level was approximately 10 mg. per hundred cubic centimeters and the serum inorganic phosphorus 1.5 mg.; the serum phosphatase activity was 15 Bodansky units. Dr. Josef Warkany reported a concentration of vitamin D in the circulating blood amounting to 150 U. S. P. units per hundred cubic centimeters of serum. No evidence was obtained of disease of the kidneys, liver or pancreas or of chronic acidosis, organic or inorganic. Anthropometric examination demonstrated that the twins were of single ovum origin.

Treatment for eight months with 50,000 U. S. P. units daily of calciferol in propylene glycol effected a transient rise of the serum phosphorus level to 3.5 mg. per hundred cubic centimeters and resulted in an increase of concentration of vitamin D to 2,600 cc. per hundred cubic centimeters of serum. The serum calcium was not affected. Frequent roentgen examination failed to reveal clearcut evidence of healing.

At this point irradiated 7-dehydrocholesterol was substituted for calciferol in the treatment of one of the twins; the dose of vitamin D was increased rapidly to 480,000 units daily. In both cases consistent and equal increase of the concentration of serum calcium and phosphorus became apparent at the level 120,000 units daily. Definite healing visible on roentgen examination did not occur until the end of an eleven day period, during which each child received 480,000 units daily. At this time the urine was loaded with amorphous phosphates and contained a large number of calcium casts. The vitamin D content of the serum was approximately 18,000 units per hundred cubic centimeters; the serum phosphorus level reached 4.5 mg. In the foregoing respects the effects of the two forms of vitamin D appeared to be identical. A single difference was found: The serum calcium level of the child who received only calciferol reached 12.2 mg., whereas that of the twin who received 7-dehydrocholesterol attained 13.5 mg. per hundred cubic centimeters. Neither child complained of subjective disturbances. When treatment was discontinued the manifestations of vitamin D intoxication receded at equal rates in the two children.

The conclusion is drawn that the two forms of vitamin D are identical in effect until toxic doses are reached. Whether the single difference that was apparent at such levels is due to properties inherent in the two substances or to the presence of contaminants, such as tachysterol, remains undetermined.

Book Reviews

Health in Schools. Twentieth Yearbook of the American Association of School Administrators, a Department of the National Education Association. Price, $2.00. Pp. 544, with 12 illustrations. Washington, D. C.: American Association of School Administrators, 1942.

A yearbook on health in the schools by the American Association of School Administrators is an event worthy of the attention of all physicians who are in earnest about trends in public health and the future of medical practice. It is the administrator of the schools who wields the greatest influence in determining school policies. His influence may determine future attitudes toward health education and medical service in the community.

Fortunately, the commission appointed to prepare this statement has not assumed that the school is the sole agency responsible for the health of the people but recognizes the role of private physicians, parents, health departments and many other agencies. There is evidence in these pages of appreciation of the fundamental principles of American medicine. The authors point out too that superstition, misinformation and ignorance about health are widespread and that the school has a serious responsibility to contribute to the preparation of the child for his life in a democracy. They stress study of the individual nature and health needs of the child and the need for more effective machinery for guidance of the health of the individual pupil. The possibilities of accurate information and the scientific basis for health practices are given appropriate attention as well as methods and conditions for sound health education.

As is usual with the report of so large a committee, the book suffers from the method of collecting manuscripts and presenting the point of view of the commission as a whole, but the plan of organization and the editing provide a generally consistent statement that should meet a need of the many school superintendents who have not been able to distinguish between sound and muddled thinking about school health programs.

Of particular interest to practicing physicians is the chapter on "Guidance of Individual Pupil Health," with its emphasis on medical history and careful study of children who are likely to be in need of medical attention. The authors point out that "the best school examination cannot take the place of the series of examinations done by the family doctor, or his alternate, the medical clinic." They indicate the trend to deemphasize the annual periodic health examination and show how "the time consumed by the annual repetition of the examinations used all possible time available of medical, dental, nursing and teaching staff." The significance of continuous observation by the teachers and screening methods are recognized as practical procedures for selecting children for guidance in a proper use of the medical facilities of the community.

The chapter on "Health Instruction and Mental Hygiene" directs attention to some of the larger possibilities for education in these fields. Less than two pages are given to the need for more education to enable children to discriminate between honest and exaggerated advertising, to counteract the appeals of faddists and quacks and to understand the dangers of self medication. So far so good, but the impact of modern advertising and unscrupulous propaganda on the American people is so tremendous in its health implications that physicians may well wish for more indications of educational procedure to meet this urgent problem.

For physicians desiring to guide school authorities toward sound policies for medical guidance in the schools, this yearbook, coming from school administrators, will probably carry more weight with the educators than recommendations coming from physicians or public health officers. While the place of the physician in

the school organization is recognized to be that of medical adviser rather than the usual position of medical examiner, there is confusion in several places as to the liaison function of the physician, but the chapter on "Coordination of Health Agencies" offers several splendid examples of plans of organization for providing medical leadership.

The 1941 Yearbook of Industrial and Orthopedic Surgery. Edited by Charles F. Painter, M.D. Price, $3.00. Pp. 432, with 353 illustrations. Chicago: The Year Book Publishers, Inc., 1941.

The author has made a comprehensive review of the recent literature (with references to previous articles) on industrial and orthopedic surgery and presented it in a small volume.

It reveals the marked advance and progress which orthopedic surgery is making from the work of the old-time so-called "harness makers" to the present day orthopedic surgeons, who have availed themselves of the development of surgical technic. Several procedures have been devised which are of assistance to the general surgeon in the selection of the proper operation for any particular patient.

The text, which is appropriately illustrated by prints of roentgenograms and photographs pertaining to the individual orthopedic subjects, is easily read and understood. The subject material includes disabilities from disease or trauma of the bones, joints, nerves and muscles, i. e. the structures of support of the body and the mechanism for function of the extremities. It contains diagnostic measures along with therapeutic suggestions.

The volume is a splendid work which would be of value not only to the orthopedic surgeon but to every general practitioner as well.

The Blood Bank and the Technique and Therapeutics of Transfusions. By Robert A. Kilduffe, M.D., and Michael DeBakey, M.D. Price, $7.50. Pp. 558, with 214 illustrations. St. Louis: C. V. Mosby Company, 1942.

The title of this very timely publication does not wholly prepare the reader for the very informative text compiled from the authors' experiences and the 2,872 references. Not alone are there contained detailed history and modern methods of every conceivable technic pertaining to blood transfusions, but there are descriptions of the physiologic aspects and brief clinical pictures of diseases and other pathologic states to which the circulating fluid is important.

As a reference on the blood bank and on technic, therapeutics and indications and contraindications for transfusions, it is excellent. The information for its readers on problems which the present emergency occasions make its appeal general.

Specifically, it is of interest to the pediatrician or the pediatric surgeon in that it presents indications and detailed methods for transfusions and associated procedures in infants, including the site of election for administration, the formula for determining replacement amounts of blood and the controversial aspects of conditions to which the administration of parenteral fluids is important.

El raquitismo en el hijo de tuberculosa. By Carlos A. Urquijo and Mario Waissmann. Price not given. Pp. 99, with 154 roentgenograms and 12 tables. Buenos Aires: El Ateneo, 1941.

This is a very interesting and thorough study on the comparative frequency of rickets in children of tuberculous mothers and in children of tuberculosis-free parents. In roentgenograms taken at birth of 93 infants whose mothers had tuberculosis, no instances of congenital rickets were found. Of 150 children of tuberculous parents, 50.4 per cent were later found to show signs of rickets, as compared with 48.8 per cent of 48 children whose parents were not tuberculous. Of the premature infants studied, 81 per cent of each group showed rickets. From this the authors conclude that tuberculosis in the mother does not affect the frequency of rickets in her children.

Directory of Pediatric Societies*

INTERNATIONAL

International Association of Preventive Pediatrics

President: Prof. S. Monrad, Dronning Louises Børnehospital, Copenhagen, Denmark.
Secretary: Dr. Daniel Oltramare, 15 Rue Lévrier, Geneva, Switzerland.

International Congress of Pediatrics

President: Dr. Henry F. Helmholz, Mayo Clinic, Rochester, Minn.
General Secretary: Dr. Kenneth D. Blackfan, 300 Longwood Ave., Boston.
Assistant Secretary-Treasurer: Dr. Charles F. McKhann, University of Michigan, Ann Arbor, Mich.

Canadian Committee:

Chairman: Dr. Alan Brown, Hospital for Sick Children, 67 College St., Toronto.
Secretary: Dr. H. P. Wright, 1509 Sherbrooke St. W., Montreal.
Place: Boston. Time: Postponed indefinitely.

International Congress for the Protection of Infancy

Secretary: Prof. G. B. Allaria, Corso Bramante 29, Torino 120, Italy.

FOREIGN

Argentine Pediatric Society of Buenos Aires

President: Dr. Martin Ramón Arana, 1809 Rodriguez Peña, Buenos Aires.
General Secretary: Dr. Alfredo Larguia, Cerrito 1179, Buenos Aires.

British Pediatric Association

President: Prof. Charles McNeil, 44 Heriot Row, Edinburgh, Scotland.
Secretary: Dr. Arthur G. Maitland Jones, 31A Weymouth St., London, W. 1.

Danish Pediatric Society

President: Dr. E. Lenstrup, Copenhagen.
Secretary: Dr. E. Gjørup, Dronning Louises Børnehospital, Copenhagen.

Nederlandische Vereeniging voor Kindergeneeskunde

President: Dr. J. H. G. Carstens, Servaasbolwerk 14ª, Utrecht, Holland.
Secretary: Dr. R. P. van de Kasteele, Laan van Poot 340, 's Gravenhage, Holland.
Place: Different places. Time: Three times a year.

Paediatrický Spolok na Slovensku

President: Dr. A. J. C. Chura, Lazaretská 11, Bratislava.
Secretary: Dr. P. Rados, Lazaretská 6, Bratislava.
Place: Pediatric Clinic, University Bratislava. Time: Six times a year.

Royal Society of Medicine, Section for the Study of Disease in Children

President: Dr. E. A. Cockayne, 98 Harley St., London, W. 1, England.
Secretary: Dr. R. Lightwood, 86 Brook St., London, W. 1, England.
Place: 1 Wimpole St., London. Time: Fourth Friday of each month, 4:15 p. m.

* Secretaries of societies are requested to furnish the information necessary to make this list complete and to keep it up to date.

PALESTINE JEWISH MEDICAL ASSOCIATION, SECTION OF PHYSICIANS OF CHILDREN'S DISEASES

President: Prof. S. Rosenbaum, 26 Bialikstr., Tel Aviv.
Secretary: Dr. A. Brünn, 9 Maazestre, Tel Aviv.

SOCIEDAD CUBANA DE PEDIATRÍA

President: Dr. Clemente Inclan Costa, Marique 48, Habana.
Secretary: Dr. Serafin Falcon Lopez, Calle B No. 356, Velado, Habana.
Place: Cátedra de Clinica Infantil, Hospital Mercedes, Habana. Time: Last Wednesday of every month.

SOCIEDAD MEXICANA DE PEDIATRIA

President: Dr. Fernando López Clares, 12/a. Medellín 191, Mexico City.
Secretary: Dr. Jesus Gómez Pagola, Versalles 64, Mexico City.

SOCIEDAD VENEZOLANA DE PUERICULTURA Y PEDIATRIA

President: Dr. Ernesto Vizcarrondo, Venezuela.
Secretary: Dr. E. Santos Mendoza, Venezuela.

SOCIÉTÉ DE PÉDIATRIE DE PARIS

President: Dr. B. Weill-Hallé, 49 Avenue Raymond Poincare, Paris, France.
Secretary: Dr. Jean Hallé, 10 bis Rue Pré aux Clercs, Paris, France.
Place: Hôpital des Enfants Malades, 49 Rue de Sèvres. Time: 4:30 p. m., third Thursday of every month.

URUGUAYAN SOCIETY OF PEDIATRICS

President: Dr. Conrado Pelfort, Av. 18 de Julio 1246, Montevideo.
Secretary: Dr. Héctor Mourigan, Ave. 18 de Julio 2175, Montevideo.

NATIONAL

AMERICAN MEDICAL ASSOCIATION, SCIENTIFIC ASSEMBLY, SECTION ON PEDIATRICS

Chairman: Dr. Philip M. Stimson, 25 Claremont Ave., New York.
Secretary: Dr. Hugh L. Dwyer, 315 Alameda Rd., Kansas City, Mo.
Place: Atlantic City. Time: June 8-12, 1942.

AMERICAN ACADEMY OF PEDIATRICS

President: Dr. Edward C. Mitchell, 1073 Madison Ave., Memphis, Tenn.
Secretary: Dr. Clifford G. Grulee, 636 Church St., Evanston, Ill.
Place: Palmer House, Chicago. Time: Nov. 4-7, 1942.
Region I. Place: Bellevue-Stratford Hotel, Philadelphia. Time: April 1-3, 1942.
Region III. Place: Hotel Cleveland, Cleveland. Time: May 14-16, 1942.
Region IV. Meeting cancelled.

AMERICAN HOSPITAL ASSOCIATION, CHILDREN'S HOSPITAL SECTION

Chairman: Dr. D. L. Richardson, 593 Eddy St., Providence, R. I.
Secretary: Dr. Joelle C. Hiebert, 299 Main St. Lewiston, Maine.

AMERICAN PEDIATRIC SOCIETY

President: Dr. Edwards A. Park, Johns Hopkins Hospital, Baltimore, Md.
Secretary-Treasurer: Dr. Hugh McCulloch, 325 N. Euclid Ave., St. Louis.
Place: Skytop Lodge, Skytop, Pa. Time: April 30–May 2, 1942.

CANADIAN SOCIETY FOR THE STUDY OF DISEASES OF CHILDREN

President: Dr. L. M. Lindsay, 815 Medical Arts Bldg., Montreal.
Secretary-Treasurer: Dr. Elizabeth Chant Robertson, Hospital for Sick Children, Toronto.

SOCIETY FOR PEDIATRIC RESEARCH

President: Dr. George M. Guest, Children's Hospital, Cincinnati.
Secretary: Dr. Mitchell I. Rubin, 1740 Bainbridge St., Philadelphia.
Place: Skytop Lodge, Skytop, Pa. Time: April 29-30, 1942.

SECTIONAL

INTERMOUNTAIN PEDIATRIC SOCIETY

President: Dr. Eugene Smith, 385–24th St., Ogden, Utah.
Secretary-Treasurer: Dr. W. C. Cheney, 837 Boston Bldg., Salt Lake City.
Place: Salt Lake City General Hospital. Time: First Thursday of each month, 8 p. m.

NEW ENGLAND PEDIATRIC SOCIETY

President: Dr. R. Cannon Eley, 319 Longwood Ave., Boston.
Secretary-Treasurer: Dr. James Marvin Baty, 319 Longwood Ave., Boston.
Place: Boston Medical Library. Time: Four meetings a year, occurring from September to May.

NORTH PACIFIC PEDIATRIC SOCIETY

President: Dr. S. G. Henricke, 4215 N. E. Hancock St., Portland, Ore.
Secretary: Dr. J. S. Backstrand, 333 Wyatt Court, Salem, Ore.

ROCKY MOUNTAIN PEDIATRIC SOCIETY

President: Dr. G. R. Fisher, 23 E. Pikes Peak Ave., Colorado Springs, Colo.
Secretary: Dr. Joseph H. Lyday, 1850 Gilpin St., Denver.
Place: Children's Hospital, Denver. Time: First Saturday of each month from September to May, inclusive, 2:30 p. m.

SOUTHERN MEDICAL ASSOCIATION, SECTION OF PEDIATRICS

Chairman: Dr. George M. Lyon, 955–4th Ave., Huntington, W. Va.
Secretary: Dr. William Weston Jr., 1428 Lady St., Columbia, S. C.

STATE

ALABAMA PEDIATRIC SOCIETY

President: Dr. M. V. Adams, 803 Government St., Mobile.
Secretary-Treasurer: Dr. William R. Britton, 4 Catoma St., Montgomery.

ARIZONA PEDIATRIC SOCIETY

President: Dr. Vivian Tappan, San Clemente, Tucson.
Secretary: Dr. Hilda Kroeger, Arizona State Health Dept. (Maternal and Child Welfare Division), Phoenix.
Place: Prescott. Time: April 1942.

ARKANSAS STATE PEDIATRIC ASSOCIATION

Chairman: Dr. C. B. Billingsley, 1425 N. 11th St., Fort Smith.
Secretary: Dr. R. E. Weddington, 1425 N. 11th St., Fort Smith.

CALIFORNIA STATE MEDICAL SOCIETY, SECTION ON PEDIATRICS

Chairman: Dr. William Belford, 233 A St., San Diego.
Secretary: Dr. John J. Miller Jr., 2398 Sacramento St., San Francisco.

FLORIDA STATE PEDIATRIC SOCIETY

President: Dr. Warren W. Quillian, 227 Aragon Ave., Coral Gables.
Secretary: Dr. George N. Leonard, 605 Lincoln Rd., Miami Beach.
Place: Concurrent with state association meeting at time of convention.

GEORGIA PEDIATRIC SOCIETY

President: Dr. R. C. McGahee, 1345 Greene St., Augusta.
Secretary-Treasurer: Dr. Don F. Cathcart, 478 Peachtree St., N. E., Atlanta.

HEZEKIAH BEARDSLEY PEDIATRIC CLUB OF CONNECTICUT

President: Dr. Ernest Caulfield, 683 Asylum Ave., Hartford.
Secretary: Dr. Edward T. Wakeman, 129 Whitney Ave., New Haven.
Time: Three meetings a year.

ILLINOIS STATE MEDICAL SOCIETY, SECTION ON PEDIATRICS

Chairman: Dr. Craig D. Butler, 715 Lake St., Oak Park.
Secretary: Dr. A. J. Fletcher, 139 N. Vermilion, Danville.
Place: Springfield. Time: May 19-21, 1942.

INDIANA STATE PEDIATRIC SOCIETY

President: Dr. K. T. Knode, 1105 E. Jefferson Blvd., South Bend.
Secretary-Treasurer: Dr. Mathew Winters, 621 Hume Mansur Bldg., Indianapolis.
Time: Two meetings a year.

IOWA PEDIATRIC SOCIETY

President: Dr. Mark L. Floyd, Children's Hospital, Iowa City.
Secretary-Treasurer: Dr. James Dunn, Davenport Bank Bldg., Davenport.

LOUISIANA STATE PEDIATRIC SOCIETY

President: Dr. S. G. Wolfe, 1560 Line Ave., Shreveport.
Secretary-Treasurer: Dr. W. C. Rivenbark, 1448 Louisiana Ave., New Orleans.

MEDICAL SOCIETY OF STATE OF NEW YORK, SECTION ON PEDIATRICS

Chairman: Dr. Norman L. Hawkins, 11 Public Sq., Watertown, N. Y.
Secretary: Dr. William J. Orr, 135 Linwood Ave., Buffalo.

MEDICAL SOCIETY OF THE STATE OF PENNSYLVANIA, PEDIATRIC SECTION

Chairman: Dr. John D. Sturgeon Jr., 22 N. Gallatin Ave., Uniontown.
Secretary: Dr. Elwood W. Stitzel, 403 Central Trust Bldg., Altoona, Pa.
Place: Pittsburgh. Time: Sept. 29-Oct. 2, 1942.

MICHIGAN STATE MEDICAL SOCIETY, PEDIATRIC SECTION

Chairman: Dr. Harry Towsley, University of Michigan Hospital, Ann Arbor.
Secretary: Dr. Leon DeVel, 110 E. Fulton, Grand Rapids.

MISSISSIPPI STATE PEDIATRIC SOCIETY

President: Dr. Harvey F. Garrison Jr., 315 E. Capitol Pl., Jackson.
Secretary: Dr. Guy Verner, 126 N. Congress St., Jackson.

NEBRASKA PEDIATRIC SOCIETY

President: Dr. Andrew G. Dow, 314 Medical Arts Bldg., Omaha.
Secretary-Treasurer: Dr. John M. Thomas, 301 N. 49th St., Omaha.
Place: As announced by Committee. Time: Third Thursday of each month from October to June, inclusive. Dinner at 6 p. m.

NEW HAMPSHIRE PEDIATRIC SOCIETY

President: Dr. MacLean J. Gill, 14 N. State St., Concord.
Secretary-Treasurer: Dr. Ursula G. Sanders, 46 Pleasant St., Concord.
Time: Twice yearly.

NORTH CAROLINA PEDIATRIC SOCIETY

President: Dr. Thomas M. Watson, Greenville.
Secretary: Dr. Frederick B. Haar, Greenville.

OKLAHOMA STATE PEDIATRIC SOCIETY

President: Dr. Ben H. Nicholson, 301 N. W. 12th St., Oklahoma City.
Secretary: Dr. Luvern Hays, 108 W. 6th St., Tulsa.
Place: Oklahoma Club. Time: 6:30 p. m., fourth Friday of each alternate month from September to May, inclusive.

SOUTH CAROLINA PEDIATRIC SOCIETY

President: Dr. R. B. Josey, 1517 Hampton Ave., Columbia.
Secretary-Treasurer: Dr. Wilson Ball, South Carolina State Health Dept., Columbia.

TENNESSEE STATE PEDIATRIC SOCIETY

President: Dr. Kinsey M. Buck, 1193 Madison Ave., Memphis.
Secretary: Dr. Gilbert Eblen, 611 W. Main Ave., Knoxville.

TEXAS PEDIATRIC SOCIETY

President: Dr. P. E. Luecke, 4105 Live Oak St., Dallas.
Secretary-Treasurer: Dr. John Ashby, 3610 Fairmount Ave., Dallas.

VIRGINIA PEDIATRIC SOCIETY

President: Dr. John M. Bishop, 511 Medical Arts Bldg., Roanoke.
Secretary: Dr. Edwin A. Harper, 301 Rivermont Ave., Lynchburg.

WEST VIRGINIA STATE MEDICAL SOCIETY, SECTION ON PEDIATRICS

President: Dr. Theresa O. Snaith, 450 Center Ave., Weston.
Secretary: Dr. Henrietta L. Marquis, 211 Bair Bldg., Beckley.

LOCAL

ACADEMY OF MEDICINE OF CLEVELAND, PEDIATRIC SECTION

Chairman: Dr. J. D. Nourse, 10515 Carnegie Ave., Cleveland.
Secretary: Dr. I. B. Silber, 10465 Carnegie Ave., Cleveland.
Place: Cleveland Medical Library Bldg. Time: October, December, February and April.

ACADEMY OF MEDICINE, TORONTO, SECTION OF PEDIATRICS

President: Dr. I. Nelles Silverthorne, 170 St. George St., Toronto, Canada.
Secretary: Dr. G. P. Hamblin, 2333 Bloor St. W., Toronto, Canada.

BRONX PEDIATRIC SOCIETY

President: Dr. David Zahn, 2474 Valentine Ave., New York.
Secretary: Dr. Harry J. Cohen, 975 Walton Ave., New York.
Place: Concourse Plaza Hotel, 161st St. and Grand Concourse. Time: Every second Wednesday of each month, except June, July, August and September.

BROOKLYN ACADEMY OF PEDIATRICS

President: Dr. Paul L. Parrish, 52 S. Oxford St., Brooklyn.
Secretary: Dr. Lewis A. Koch, 62 Pierrepont St., Brooklyn.
Place: Granada Hotel. Time: Fourth Wednesday of each month, except May, June, July, August and September.

Buffalo Pediatric Society

President: Dr. A. Wilmot Jacobsen, 187 Bryant St., Buffalo, N. Y.
Secretary: Dr. Richard A. Downey, 786 Forest Ave., Buffalo, N. Y.
Place: Children's Hospital, 219 Bryant St. Time: 8:30 p. m., first Monday of each month from September to June.

Central New York Pediatric Club

President: Dr. Frank van der Bogert, 111 Union St., Schenectady.
Secretary: Dr. Frank J. Williams, 58 S. Swan St., Albany.
Places: Various cities in New York. Time: Third Tuesday of April and September.

Chicago Pediatric Society

President: Dr. James H. Wallace, 715 Lake St., Oak Park, Ill.
Secretary: Dr. Henry G. Poncher, 1819 W. Polk St., Chicago.
Place: Children's Memorial Hospital, 710 Fullerton Ave. Time: Third Tuesday of each month, October to May, inclusive.

Cincinnati Pediatric Society

President: Dr. Lloyd K. Felter, 3144 Jefferson Ave., Cincinnati.
Secretary: Dr. Leo S. Friedman, 3586 Reading Rd., Cincinnati.
Place: Children's Hospital, Elland Ave., Cincinnati. Time: On call.

Dallas Pediatric Society

President: Dr. Bruce A. Knickerbocker, 3403 Hall St., Dallas, Texas.
Secretary-Treasurer: Dr. Floyd A. Norman, 4325 Cole Ave., Dallas, Texas.
Place: Bradford Baby Hospital. Time: 1 p. m., second and fourth Saturdays of each month.

Detroit Pediatric Society

President: Dr. Marsh M. Poole, 773 Fisher Bldg., Detroit, Mich.
Secretary: Dr. Donald J. Barnes, 773 Fisher Bldg., Detroit, Mich.
Place: Wayne County Medical Society. Time: 8:30 p. m., first Wednesday of each month from October to June, inclusive.

Fulton County Medical Society, Pediatrics Section (Atlanta, Ga.)

Chairman: Dr. Don F. Cathcart, 478 Peachtree St. N. E., Atlanta.
Secretary: Dr. Harry Lange, 478 Peachtree St. N. E., Atlanta.
Place: Academy of Medicine, 38 Prescott St. N. E. Time: Second Thursday of each month from October to April, 8 p. m.

Houston Pediatric Society

President: Dr. Raymond Cohen, 2300 Caroline St., Houston, Texas.
Secretary: Dr. Betty Moody, 526 Richmond Rd., Houston, Texas.
Place: College Inn, Houston. Time: Fourth Monday of each month.

Kansas City (Missouri) Pediatric Society

President: Dr. Edwin H. Schorer, 1103 Grand Ave., Kansas City.
Secretary: Dr. H. E. Petersen, Physician's and Surgeon's Bldg., St. Joseph, Mo.
Place: Kansas City General Hospital. Time: On call.

Los Angeles County Medical Association, Pediatric Section

President: Dr. Alonzo Cass, 1908 Wilshire Blvd., Los Angeles.
Secretary-Treasurer: Dr. Gladys Patric Shahovitch, 3936 Roderick Rd., Los Angeles.
Place: Los Angeles County Medical Headquarters, 1925 Wilshire Blvd. Time: Second Monday of February, April, June, October and December.

Medical Society of the County of Kings and the Academy of Medicine of Brooklyn, Pediatric Section

President: Dr. Sydney Nussbaum, 247 Ocean View Ave., Brooklyn.
Secretary: Dr. Harry S. Bikoff, 850 St. Marks Ave., Brooklyn.
Place: 1313 Bedford Ave., Brooklyn. Time: 9:00 p. m., fourth Monday of each month, October to April, inclusive.

Medical Society of the County of Queens, Inc., Section on Pediatrics

Chairman: Dr. A. A. Trivilino, 88-07–150th St., Jamaica, N. Y.
Secretary-Treasurer: Dr. Edith A. Mittell, 144–38th Ave., Flushing, N. Y.
Place: Queens County Medical Bldg., Forest Hills, N. Y. Time: Third Monday of October, January, March and May.

Medical Society of the District of Columbia, Section on Pediatrics

President: Dr. James M. Moser, 3751 Jenifer St. N. W., Washington, D. C.
Secretary-Treasurer: Dr. William A. Howard, 2222 Que St. N. W., Washington, D. C.
Place: Medical Society Bldg., 1718 M St. N. W. Time: 8 p. m., fourth Thursday of every month.

Memphis Pediatric Society

President: Dr. E. C. Mitchell, 1073 Madison Ave., Memphis, Tenn.
Secretary-Treasurer: Dr. Harry Jacobson, 1193 Madison Ave., Memphis, Tenn.
Place: John Gaston Hospital. Time: Quarterly.

Milwaukee Pediatric Society

President: Dr. John H. Reynolds, 1628 W. Wisconsin Ave., Milwaukee.
Secretary-Treasurer: Dr. F. J. Mellencamp, 324 E. Wisconsin Ave., Milwaukee.
Place: Milwaukee Athletic Club. Time: Second Wednesday of each alternate month, beginning with February.

New York Academy of Medicine, Section of Pediatrics

Chairman: Dr. Alfred Langmann, 108 E. 68th St., New York.
Secretary: Dr. Edith M. Lincoln, 600 Park Ave., New York.
Place: New York Academy of Medicine, 2 E. 103d St. Time: Second Thursday of each month from October to May, inclusive, 8:30 p. m.

Northern California Affiliates

President: Dr. Crawford Bost, 490 Post St., San Francisco.
Secretary: Dr. William A. Reilly, 384 Post St., San Francisco.
Time: Second Thursday of September, November, January, March and May.

Northwestern Pediatric Society

President: Dr. John M. Adams, 1009 Nicollet Ave., Minneapolis.
Secretary-Treasurer: Dr. Albert V. Stoesser, 205 W. University Hospital, Minneapolis.
Place: Minneapolis, St. Paul, Duluth and Rochester. Time: January, April, July and October.

Oklahoma City Pediatric Society

President: Dr. J. Byron Snow, 1200 N. Walker St., Oklahoma City.
Secretary: Dr. G. R. Felts, 1200 N. Walker St., Oklahoma City.
Place: Oklahoma Club. Time: Fourth Friday of each alternate month.

Philadelphia Pediatric Society

President: Dr. Paul B. Cassidy, 2037 Pine St., Philadelphia.
Secretary: Dr. Aims C. McGuinness, Children's Hospital, 1740 Bainbridge St., Philadelphia.
Place: College of Physicians, 19 S. 22d St. Time: Second Tuesday of each month from October to April, inclusive.

Pittsburgh Pediatric Society

President: Dr. Ellsmer L. Piper, 3708–5th Ave., Pittsburgh.
Secretary-Treasurer: Dr. Carl Ruder, 646 Washington Rd., Mount Lebanon, Pittsburgh.
Place: Pittsburgh Academy of Medicine. Time: Second Friday, alternate month from October to June, inclusive.

Richmond Pediatric Society

President: Dr. Stanley Meade, 913 Floyd Ave., Richmond, Va.
Secretary-Treasurer: Dr. Herman W. Farber, 501 E. Franklin St., Richmond, Va.
Place: Richmond Academy of Medicine, 1200 E. Clay St. Time: 8 p. m., third Thursday of each month, except June, July and August.

Rochester Pediatric Society

President: Dr. Herbert Soule, 122 Rutgers St., Rochester, N. Y.
Secretary-Treasurer: Dr. Jerome Glaser, 300 S. Goodman St., Rochester, N. Y.
Place: Rochester Academy of Medicine or arrangement by program committee. Time: Third Friday of each month from October to May.

St. Louis Pediatric Society

President: Dr. Maurice J. Lonsway, 3720 Washington Blvd., St. Louis.
Secretary-Treasurer: Dr. Mary A. McLoon, 408 Humboldt Bldg., St. Louis.
Place: St. Louis Medical Society Bldg. Time: First Friday of each month from October to June.

Seattle Pediatric Society

President: Dr. Frederick B. Joy, Stimson Bldg., Seattle.
Secretary: Dr. Sherod M. Billington, Medical Dental Bldg., Seattle.
Place: College Club. Time: Third Friday of each month from September to June at 6:30 p. m.

Southwestern Pediatric Society

President: Dr. Norman Nixon, 1136 W. 6th St., Los Angeles.
Secretary: Dr. Donald C. Shelby, 3780 Wilshire Blvd., Los Angeles.
Place: Jonathan Club of Los Angeles. Time: First Wednesday in January, March, May, September and November.

University of Michigan Pediatric and Infectious Disease Society

President: Dr. Campbell Harvey, 35 W. Huron St., Pontiac, Mich.
Secretary: Dr. Harry A. Towsley, University of Michigan, Department of Pediatrics and Communicable Diseases, Ann Arbor, Mich.

Westchester County Medical Society, Pediatrics Section (New York)

President: Dr. John B. Ahouse, 27 Ludlow St., Yonkers, N. Y.
Secretary-Treasurer: Dr. Elvira Ostlund, 64 Highland Rd., Rye.
Place: Grasslands Hospital, Valhalla, N. Y. Time: Third Thursday in October, December, February and April.